PYRAZOLINES AS PAR-1-ANTAGONISTS FOR TREATING CARDIOVASCULAR DISORDERS

The present invention relates to the field of blood coagulation. The present invention relates in particular to the use of pyrazolines as medicaments, to novel pyrazolines and to processes for their preparation, and also to their use for preparing medicaments for the treatment and/or prophylaxis of diseases, in particular cardiovascular disorders, preferably thromboembolic disorders.

Thrombocytes (blood platelets) are an essential factor both in physiological suppression of bleeding (haemostasis) and in thromboembolic disorders. In particular in the arterial system, platelets play a central role in the complex interaction between blood components and the wall of blood vessels. Unwanted platelet activation may, as a result of the formation of platelet-rich thrombi, lead to thromboembolic disorders and thrombotic complications with life-threatening conditions.

One of the most potent platelet activators is the coagulation protease thrombin which is formed on injured walls of blood vessels and which, in addition to forming fibrin, activates platelets, endothelial cells and mesenchymal cells (Vu TKH, Hung DT, Wheaton VI, Coughlin SR, *Cell* 1991, *64*, 1057-1068). In platelets in vitro and in animal models, thrombin inhibitors inhibit platelet aggregation and the formation of platelet-rich thrombi. In humans, arterial thromboses can be treated successfully with inhibitors of platelet function and thrombin inhibitors (Bhatt DL, Topol EJ, *Nat. Rev. Drug Discov.* 2003, *2*, 15-28). Accordingly, there is a high probability that antatonists of the effect of thrombin on blood platelets reduce the formation of thrombi and the occurrence of clinical sequelae, such as myocardial infarction and stroke. Further cellular thrombin actions, for example on endothelial and smooth muscle cells of blood vessels, on leukocytes and on fibroblasts, are possibly responsible for inflammatory and proliferative disorders.

At least in part, the cellular effects of thrombin are mediated via a family of G-protein-coupled receptors (Protease Activated Receptors, PARs), the prototype of which is the PAR-1 receptor. PAR-1 is activated by binding of thrombin and proteolytic cleavage of its extracellular N-terminus. The proteolysis exposes a new N-terminal with the amino acid sequence SFLLRN... which, as agonist ("Tethered Ligand") leads to intramolecular receptor activation and transmission of intracellular signals. Peptides derived from the Tethered-Ligand sequence can be employed as agonists of the receptor and, on platelets, lead to activation and aggregation.

Antibodies and other selective PAR-1 antagonists inhibit the thrombin-induced aggregation of platelets in vitro at low to medium thrombin concentrations (Kahn ML, Nakanishi-Matsui M, Shapiro MJ, Ishihara H, Coughlin SR, *J. Clin. Invest.* 1999, *103*, 879-887). A further thrombin

receptor of possible importance for the pathophysiology of thrombotic processes, PAR-4, has been identified on human and animal platelets. In experimental thromboses in animals having a PAR expression pattern similar to that of humans, PAR-1 antagonists reduce the formation of platelet-rich thrombi (Derian CK, Damiano BP, Addo MF, Darrow AL, D'Andrea MR, Nedelman M, Zhang H-C, Maryanoff BE, Andrade-Gordon P, *J. Pharmacol. Exp. Ther.* 2003, *304*, 855-861).

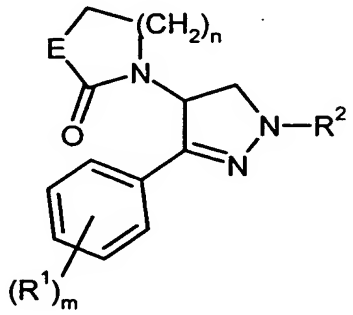
Lately, a large number of substances have been examined for their platelet function-inhbiting action. In practice, only few platelet function inhibitors have been found to be useful. Accordingly, there is a need for pharmaceutics which specifically inhibit a heightened platelet reaction without significantly increasing the risk of bleeding, thus reducing the risk of thromboembolic complications. In contrast to the inhibition of the protease activity of thrombin using direct thrombin inhibitors, a blockade of PAR-1 should result in an inhibition of platelet activation without reduction of the coagulability of the blood.

Accordingly, it is an object of the present invention to provide novel PAR-1 antagonists for treating cardiovascular disorders, such as, for example, thromboembolic disorders, in humans and animals.

EP-A 466 408, EP-A 438 690, EP-A 532 918 and WO 93/24463 describe pyrazoline derivatives of a similar structure and their use as pesticides.

WO 02/00651 describes pyrazoline derivatives as factor Xa inhibitors for treating thromboembolic disorders.

The present invention provides compounds of the formula



(I),

in which

E represents methylene, NH, an oxygen atom or a sulphur atom,

m represents 0, 1, 2 or 3,

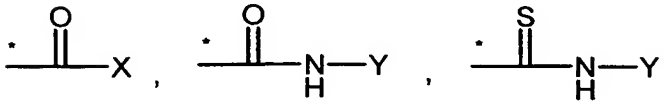
n represents 1, 2 or 3,

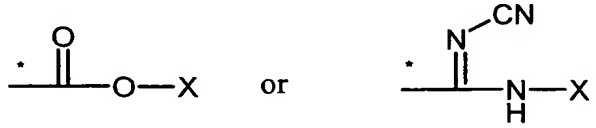
R^1 represents halogen, hydroxyl, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, hydroxycarbonyl, aminocarbonyl, alkoxycarbonyl, alkylaminocarbonyl or $-NH(C=O)OR^9$,

where

R^9 represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_6-C_{10})-aryl, (C_3-C_7)-cycloalkyl-methyl or (C_6-C_{10})-arylmethyl,

R^2 represents a group of the formula





where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or (C_1-C_8)-alkylene-R^4,

where alkylene may be substituted by 1 to 4 fluorine atoms,

Y represents R^3 or (C_1-C_8)-alkylene-R^4,

where alkylene may be substituted by 1 to 4 fluorine atoms,

R^3 represents 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, indanyl, 1,2,3,4-tetrahydronaphthyl, (C_6-C_{10})-aryl, 5- to 10-membered heteroaryl, (C_3-C_6)-cycloalkyl or 5- to 10-membered heterocyclyl,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy,

trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^4 represents hydrogen, 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, indanyl, 1,2,3,4-tetrahydronaphthyl, $(C_6$-$C_{10})$-aryl, 5- to 10-membered heteroaryl, $(C_3$-$C_7)$-cycloalkyl, 5- to 10-membered heterocyclyl, hydroxyl, cyano, trifluoromethyl, optionally fluorine-substituted alkylthio, $-OR^5$, $-C(=O)R^6$ or $-NR^7R^8$,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, oxo, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, optionally alkoxycarbonyl-substituted alkoxy, alkylamino, aryl, benzyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^5 represents optionally fluorine-substituted alkyl, $(C_6$-$C_{10})$-aryl, benzyl, $(C_3$-$C_7)$-cycloalkyl or alkylcarbonyl,

where aryl, benzyl or cycloalkyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, oxo, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, benzyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^6 represents hydroxyl, amino, alkyl, alkylamino, alkoxy, $(C_6$-$C_{10})$-aryl, benzyloxy or 5- to 10-membered heterocyclyl,

where aryl or benzyloxy may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, oxo, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, benzyl, hydroxycarbonyl,

alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^7 represents hydrogen, alkyl or benzyl,

R^8 represents hydrogen, alkyl, phenyl, alkylcarbonyl, alkoxycarbonyl, alkylsulphonyl, optionally alkyl-substituted arylcarbonyl or optionally alkyl-substituted arylsulphonyl,

and their salts, their solvates and the solvates of their salts

for the treatment and/or prophylaxis of diseases, in particular cardiovascular disorders, such as, for example, thromboembolic disorders.

Compounds according to the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts; the compounds of the formulae below encompassed by formula (I) and their salts, solvates and solvates of the salts, and also the compounds mentioned below as working examples encompassed by formula (I) and their salts, solvates and solvates of the salts, if the compounds mentioned below encompassed by formula (I) are not already salts, solvates and solvates of the salts.

Depending on their structure, the compounds according to the invention can exist in stereoisomeric forms (enantiomers, diastereomers). Accordingly, the invention embraces the enantiomers or diastereomers and their respective mixtures. From such mixtures of enantiomers and/or diastereomers, the stereoisomerically uniform components can be isolated in a known manner.

If the compounds according to the invention may be present in tautomeric forms, the present invention encompasses all tautomeric forms.

In the context of the present invention, preferred salts are physiologically acceptable salts of the compounds according to the invention. However, also encompassed are salts which for their part are not suitable for pharmaceutical applications but which can be used, for example, for isolating or purifying the compounds according to the invention.

Physiologically acceptable salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds according to the invention also include salts of customary bases, such as, by way of example and by way of preference, alkali metal salts (for example sodium and potassium salts), alkaline earth metal salts (for example calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and by way of preference, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, ethylenediamine and *N*-methylpiperidine.

In the context of the invention, solvates are forms of the compounds according to the invention which, in the solid or liquid state, form a complex by coordination with solvent molecules. Hydrates are a specific form of solvates where the coordination is with water.

In the context of the present invention, the substituents are as defined below, unless specified otherwise:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkoxycarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl represent a straight-chain or branched alkyl radical having 1 to 8, generally 1 to 6, preferably 1 to 4, particularly preferably 1 to 3, carbon atoms, by way of example and by way of preference methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, *n*-pentyl and *n*-hexyl.

Alkylene represents a straight-chain or branched alkylene radical having generally 1 to 8, preferably 1 to 6, carbon atoms which optionally contains one or more double or triple bonds. Methylene, ethylene, propylene, propane-1,2-diyl, propane-2,2-diyl, butane-1,3-diyl, butane-2,4-diyl, pentane-2,4-diyl, 2-methylpentane-2,4-diyl may be mentioned by way of example and by way of preference.

Alkoxy represents, by way of example and by way of preference, methoxy, ethoxy, *n*-propoxy, isopropoxy, *tert*-butoxy, *n*-pentoxy and *n*-hexoxy.

Alkylamino represents an alkylamino radical having one or two (selected independently of one another) alkyl substituents, by way of example and by way of preference methylamino, ethylamino, *n*-propylamino, isopropylamino, *tert*-butylamino, *n*-pentylamino, *n*-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-*n*-propylamino, *N*-isopropyl-*N*-*n*-propylamino, *N*-*tert*-butyl-*N*-methylamino, *N*-ethyl-*N*-*n*-pentylamino and *N*-*n*-hexyl-*N*-methylamino. C_1-C_3-Alkylamino represents, for example, a monoalkylamino radical having 1 to 3 carbon atoms or represents a dialkylamino radical having in each case 1 to 3 carbon atoms per alkyl substituent.

Alkoxycarbonyl represents, by way of example and by way of preference, methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, *n*-pentoxycarbonyl and *n*-hexoxycarbonyl.

Alkylaminocarbonyl represents an alkylaminocarbonyl radical having one or two (selected independently of one another) alkyl substituents, where the alkyl substituents, independently of one another, generally have 1 to 6, preferably 1 to 4, particularly preferably 1 to 3, carbon atoms, by way of example and by way of preference methylaminocarbonyl, ethylaminocarbonyl, *n*-propylaminocarbonyl, isopropylaminocarbonyl, *tert*-butylaminocarbonyl, *n*-pentylaminocarbonyl, *n*-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-*n*-propylaminocarbonyl, *N*-isopropyl-*N*-*n*-propylaminocarbonyl, *N*-*tert*-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-*n*-pentylaminocarbonyl and *N*-*n*-hexyl-*N*-methylaminocarbonyl. C_1-C_3-Alkylaminocarbonyl represents, for example, a monoalkylaminocarbonyl radical having 1 to 3 carbon atoms or represents a dialkylaminocarbonyl radical having in each case 1 to 3 carbon atoms per alkyl substituent.

Alkylcarbonyl represents, by way of example and by way of preference, methylcarbonyl, ethylcarbonyl, *n*-propylcarbonyl, isopropylcarbonyl, *tert*-butylcarbonyl, *n*-pentylcarbonyl and *n*-hexylcarbonyl.

Alkylcarbonyloxy represents, by way of example and by way of preference, methylcarbonyloxy, ethylcarbonyloxy, *n*-propylcarbonyloxy, isopropylcarbonyloxy, *tert*-butylcarbonyloxy, *n*-pentylcarbonyloxy and *n*-hexylcarbonyloxy.

Alkylcarbonylamino represents, by way of example and by way of preference, methylcarbonylamino, ethylcarbonylamino, *n*-propylcarbonylamino, isopropylcarbonylamino, *tert*-butylcarbonylamino, *n*-pentylcarbonylamino and *n*-hexylcarbonylamino.

Alkylsulphonyl represents, by way of example and by way of preference, methylsulphonyl, ethylsulphonyl, *n*-propylsulphonyl, isopropylsulphonyl, *tert*-butylsulphonyl, *n*-pentylsulphonyl and *n*-hexylsulphonyl.

cycloalkyl represents a mono- or bicyclic cycloalkyl group having generally 3 to 8, preferably 5 or 6 carbon atoms, by way of example and by way of preference, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and norbornyl may be mentioned for cycloalkyl.

Aryl per se and "aryl" in aryloxy and arylcarbonylamino represents a mono- to tricyclic aromatic radical having generally 6 to 14, preferably 6 to 10, carbon atoms, by way of example and by way of preference phenyl, naphthyl and phenanthrenyl.

Aryloxy represents, by way of example and by way of preference, phenyloxy and naphthyloxy.

Arylcarbonylamino represents, by way of example and by way of preference, phenylcarbonylamino and naphthylcarbonylamino.

Heteroaryl represents an aromatic mono- or bicyclic radical having generally 5 to 10, preferably 5 or 6, ring atoms and up to 5, preferably up to 4, heteroatoms from the group consisting of S, O and N, by way of example and by way of preference thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazolyl, imidazolyl, triazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Heterocyclyl represents an optionally benzo-fused mono- or bicyclic heterocyclic radical having generally 3 to 10, preferably 5 to 10, in particular 5 or 6, ring atoms and up to 3, preferably up to 2, heteroatoms and/or hetero groups from the group consisting of N, O, S, SO, SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the group consisting of O, N and S, by way of example and by way of preference oxetan-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, tetrahydrofuranyl, tetrahydrothienyl, pyranyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, thiopyranyl, morpholin-1-yl, morpholin-2-yl, morpholin-3-yl, perhydroazepinyl, piperazin-1-yl, piperazin-2-yl.

Halogen represents fluorine, chlorine, bromine and iodine, preferably fluorine and chlorine.

A symbol # at a carbon atom means that the compound, with respect to its configuration at this carbon atom, is present in enantiomerically pure form, which, in the context of the present invention, is to be understood as meaning an enantiomeric excess of more than 90% (> 90% ee).

If radicals in the compounds of the formula (I), their salts, their solvates or the solvates of their salts are substituted, the radicals may, unless specified otherwise, be mono- or polysubstituted by identical or different substituents. Preference is given to a substitution with up to three identical or different substituents. Very particular preference is given to the substitution with one substituent.

The present invention furthermore provides compounds of the formula (I),

in which

E represents methylene, NH, an oxygen atom or a sulphur atom,

m represents 0, 1, 2 or 3,

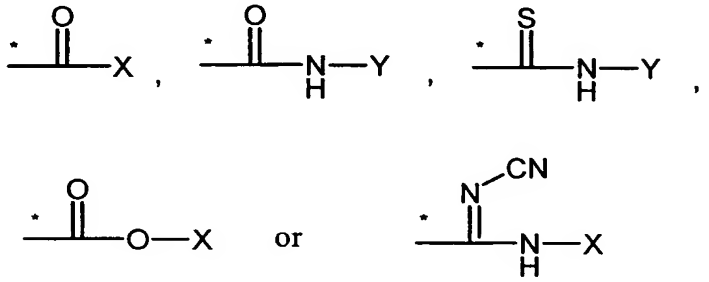
n represents 1, 2 or 3,

R^1 represents halogen, hydroxyl, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, hydroxycarbonyl, aminocarbonyl, alkoxycarbonyl, alkylaminocarbonyl or $-NH(C=O)OR^9$,

where

R^9 represents (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_6-C_{10})-aryl, (C_3-C_7)-cycloalkyl-methyl or (C_6-C_{10})-arylmethyl,

R^2 represents a group of the formula



where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or (C_1-C_8)-alkylene-R^4,

where alkylene may be substituted by 1 to 4 fluorine atoms,

Y represents (C_1-C_8)-alkylene-R^4,

where alkylene may be substituted by 1 to 4 fluorine atoms,

R^3 represents 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, indanyl, 1,2,3,4-tetrahydronaphthyl, (C_6-C_{10})-aryl, 5- to 10-membered heteroaryl, (C_3-C_6)-cycloalkyl or 5- to 10-membered heterocyclyl,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy,

trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^4 represents hydrogen, 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, indanyl, 1,2,3,4-tetrahydronaphthyl, (C_6-C_{10})-aryl, 5- to 10-membered heteroaryl, (C_3-C_7)-cycloalkyl, 5- to 10-membered heterocyclyl, hydroxyl, cyano, trifluoromethyl, optionally fluorine-substituted alkylthio, $-OR^5$, $-C(=O)R^6$ or $-NR^7R^8$,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, oxo, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, optionally alkoxycarbonyl-substituted alkoxy, alkylamino, aryl, benzyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^5 represents optionally fluorine-substituted alkyl, (C_6-C_{10})-aryl, benzyl, (C_3-C_7)-cycloalkyl or alkylcarbonyl,

where aryl, benzyl or cycloalkyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, oxo, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, benzyl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^6 represents hydroxyl, amino, alkyl, alkylamino, alkoxy, (C_6-C_{10})-aryl, benzyloxy or 5- to 10-membered heterocyclyl,

where aryl or benzyloxy may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, oxo, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, benzyl, hydroxycarbonyl,

alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^7 represents hydrogen, alkyl or benzyl,

R^8 represents hydrogen, alkyl, phenyl, alkylcarbonyl, alkoxycarbonyl, alkylsulphonyl, optionally alkyl-substituted arylcarbonyl or optionally alkyl-substituted arylsulphonyl,

and their salts, their solvates and the solvates of their salts.

Preference is given to compounds of the formula (I)

in which

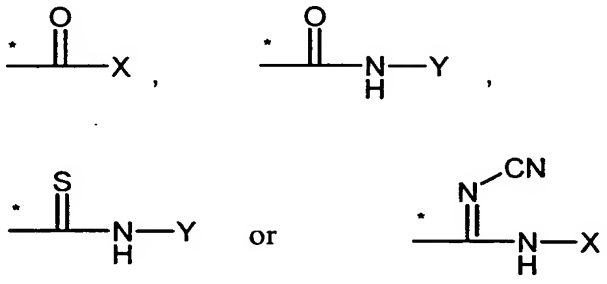
E represents methylene, NH or an oxygen atom,

m represents 0, 1 or 2,

n represents 1, 2 or 3,

R^1 represents halogen, amino, cyano, nitro, trifluoromethyl, alkyl or alkoxy,

R^2 represents a group of the formula



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Y represents $(C_1\text{-}C_8)$-alkylene-R^4,

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tetrahydronaphthyl, phenyl, 5- or 6-membered heteroaryl, (C_3-C_6)-cycloalkyl or 5- or 6-membered heterocyclyl,

where phenyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, trichloromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylamino, phenyl, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, (C_1-C_4)-alkylaminocarbonyl and (C_1-C_4)-alkylcarbonyl,

R^4 represents hydrogen, 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, indanyl, 1,2,3,4-tetrahydronaphthyl, phenyl, naphthyl, 5- or 6-membered heteroaryl, (C_5-C_6)-cycloalkyl, 5- or 6-membered heterocyclyl, cyano, trifluoromethyl, $-OR^5$, $-C(=O)R^6$ or $-NR^7R^8$,

where phenyl, naphthyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, oxo, trichloromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylamino, phenyl, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, (C_1-C_4)-alkylaminocarbonyl and (C_1-C_4)-alkylcarbonyl,

R^5 represents optionally fluorine-substituted (C_1-C_4)-alkyl, phenyl, benzyl or (C_1-C_4)-alkylcarbonyl,

R^6 represents (C_1-C_4)-alkoxy,

R^7 represents hydrogen or (C_1-C_4)-alkyl,

R^8 represents (C_1-C_4)-alkyl or optionally (C_1-C_4)-alkyl-substituted phenylcarbonyl,

and their salts, their solvates and the solvates of their salts.

Particular preference is given to compounds of the formula (I),

in which

E represents methylene, NH or an oxygen atom,

m represents 0, 1 or 2,

n represents 1, 2 or 3,

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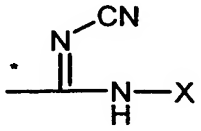
R^2 represents a group of the formula



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R^3 represents 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, phenyl, 5- or 6-membered heteroaryl or (C_3-C_6)-cycloalkyl,

where phenyl, heteroaryl or cycloalkyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of halogen, cyano, trichloromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 represents hydrogen, phenyl, 5- or 6-membered heteroaryl, (C_5-C_6)-cycloalkyl, 5- or 6-membered heterocyclyl, cyano, trifluoromethyl, $-OR^5$ or $-NR^7R^8$,

where phenyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of halogen, cyano, oxo, trichloromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^5 represents optionally fluorine-substituted (C_1-C_4)-alkyl,

R^7 represents hydrogen or (C_1-C_4)-alkyl,

R^8 represents (C_1-C_4)-alkyl,

and their salts, their solvates and the solvates of their salts.

Very particular preference is given to compounds of the formula (I),

in which

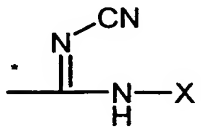
E represents methylene,

m represents 1,

n represents 1,

R^1 represents halogen,

R^2 represents a group of the formula



where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or (C_1-C_6)-alkylene-R^4,

R^3 represents phenyl, 5- or 6-membered heteroaryl or (C_5-C_6)-cycloalkyl,

where phenyl, heteroaryl or cycloalkyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of halogen, cyano, trichloromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 represents hydrogen, phenyl, 5- or 6-membered heteroaryl, (C_5-C_6)-cycloalkyl, 5- or 6-membered heterocyclyl, cyano, trifluoromethyl or $-OR^5$,

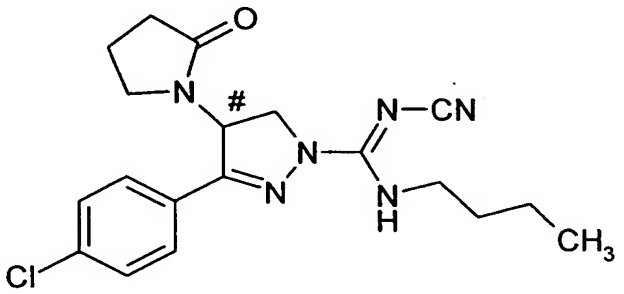
where phenyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 or 2 substituents independently of one another selected from the group

consisting of halogen, cyano, trichloromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

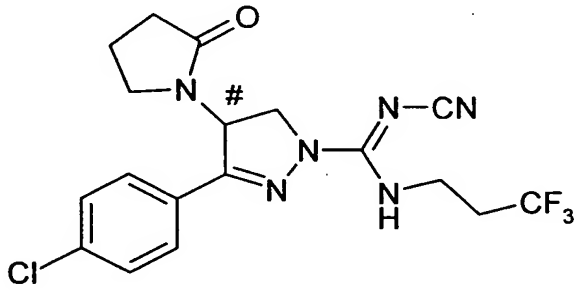
R^5 represents methyl or ethyl,

and their salts, their solvates and the solvates of their salts.

Particular preference is given to the compound *N*-butyl-3-(4-chlorophenyl)-*N'*-cyano-4-(2-oxo-pyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



Particular preference is likewise given to the compound 3-(4-chlorophenyl)-*N'*-cyano-4-(2-oxo-pyrrolidin-1-yl)-*N*-(3,3,3-trifluoropropyl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



The present invention furthermore provides compounds of the formula (I),

in which

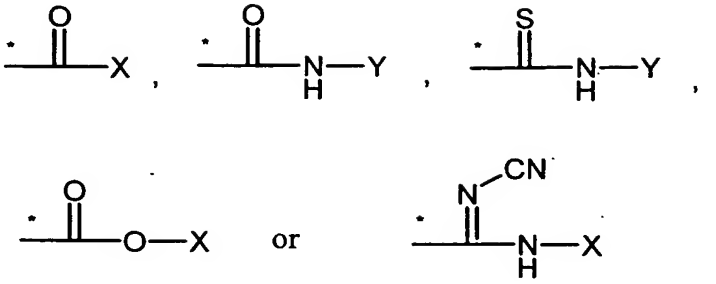
E represents methylene, NH, an oxygen atom or a sulphur atom,

m represents 0, 1, 2 or 3,

n represents 1, 2 or 3,

R^1 represents halogen, hydroxyl, amino, cyano, nitro, alkyl, alkoxy, hydroxycarbonyl, aminocarbonyl, alkoxycarbonyl or alkylaminocarbonyl,

R^2 represents a group of the formula



where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or $(C_1\text{-}C_8)$-alkylene-R^4,

Y represents R^3 or $(C_1\text{-}C_8)$-alkylene-R^4,

R^3 represents 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, $(C_6\text{-}C_{10})$-aryl, 5- to 10-membered heteroaryl, $(C_3\text{-}C_6)$-cycloalkyl or 5- to 10-membered heterocyclyl,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^4 represents hydrogen, 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, $(C_6\text{-}C_{10})$-aryl, $(C_6\text{-}C_{10})$-aryloxy, benzyloxy, 5- to 10-membered heteroaryl, $(C_3\text{-}C_7)$-cycloalkyl, 5- to 10-membered heterocyclyl, hydroxyl, amino, alkoxy, alkylamino, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylamino, optionally alkyl-substituted arylcarbonylamino or alkylcarbonyloxy,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of

hydroxyl, amino, halogen, cyano, nitro, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

and their salts, their solvates and the solvates of their salts

for the treatment and/or prophylaxis of diseases, in particular cardiovascular disorders, such as, for example, thromboembolic disorders.

The present invention furthermore provides compounds of the formula (I),

in which

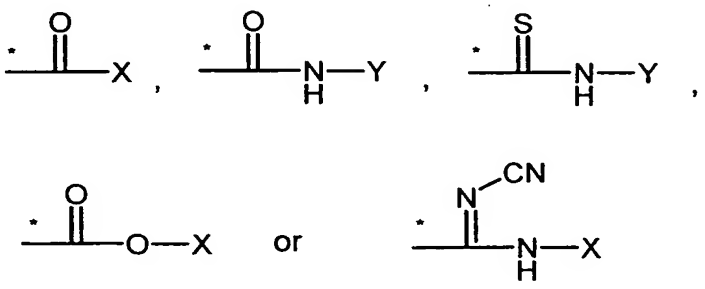
E represents methylene, NH, an oxygen atom or a sulphur atom,

m represents 0, 1, 2 or 3,

n represents 1, 2 or 3,

R^1 represents halogen, hydroxyl, amino, cyano, nitro, alkyl, alkoxy, hydroxycarbonyl, aminocarbonyl, alkoxycarbonyl or alkylaminocarbonyl,

R^2 represents a group of the formula



where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or $(C_1\text{-}C_8)$-alkylene-R^4,

Y represents $(C_1\text{-}C_8)$-alkylene-R^4,

R^3 represents 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, (C_6-C_{10})-aryl, 5- to 10-membered heteroaryl, (C_3-C_6)-cycloalkyl or 5- to 10-membered heterocyclyl,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

R^4 represents hydrogen, 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, (C_6-C_{10})-aryl, (C_6-C_{10})-aryloxy, benzyloxy, 5- to 10-membered heteroaryl, (C_3-C_7)-cycloalkyl, 5- to 10-membered heterocyclyl, hydroxyl, amino, alkoxy, alkylamino, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonylamino, optionally alkyl-substituted arylcarbonylamino or alkylcarbonyloxy,

where aryl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, monohalomethyl, dihalomethyl, trihalomethyl, monohalomethoxy, dihalomethoxy, trihalomethoxy, alkyl, alkoxy, alkylamino, aryl, hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonylamino and alkylsulphonyl,

and their salts, their solvates and the solvates of their salts.

Preference is given to compounds of the formula (I)

in which

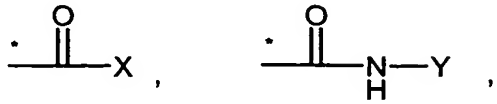
E represents methylene, NH or an oxygen atom,

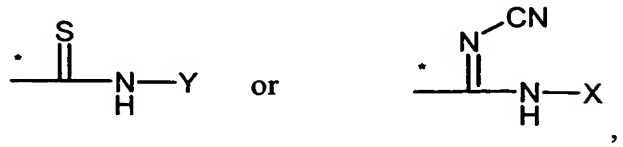
m represents 0, 1 or 2,

n represents 1, 2 or 3,

R^1 represents halogen, cyano, nitro, alkyl or alkoxy,

R^2 represents a group of the formula





where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or $(C_1\text{-}C_8)$-alkylene-R^4,

Y represents $(C_1\text{-}C_8)$-alkylene-R^4,

R^3 represents 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, phenyl, 5- or 6-membered heteroaryl, $(C_5\text{-}C_6)$-cycloalkyl or 5- or 6-membered heterocyclyl,

where phenyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, trichloromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxy, $(C_1\text{-}C_4)$-alkylamino, phenyl, hydroxycarbonyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, aminocarbonyl, $(C_1\text{-}C_4)$-alkylaminocarbonyl and $(C_1\text{-}C_4)$-alkylcarbonyl,

R^4 represents hydrogen, 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, phenyl, naphthyl, phenyloxy, benzyloxy, 5- or 6-membered heteroaryl, $(C_5\text{-}C_6)$-cycloalkyl, 5- or 6-membered heterocyclyl, $(C_1\text{-}C_4)$-alkoxy, $(C_1\text{-}C_4)$-alkylamino, $(C_1\text{-}C_4)$-alkoxycarbonyl, optionally $(C_1\text{-}C_4)$-alkyl-substituted phenylcarbonylamino or $(C_1\text{-}C_4)$-alkylcarbonyloxy,

where phenyl, naphthyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 to 3 substituents independently of one another selected from the group consisting of hydroxyl, amino, halogen, cyano, nitro, trichloromethyl,

trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylamino, phenyl, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, (C_1-C_4)-alkylaminocarbonyl and (C_1-C_4)-alkylcarbonyl,

and their salts, their solvates and the solvates of their salts.

Particular preference is given to compounds of the formula (I)

in which

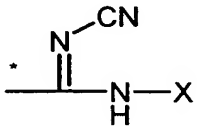
E represents methylene, NH or an oxygen atom,

m represents 0 or 1,

n represents 1, 2 or 3,

R^1 represents halogen, cyano, (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy,

R^2 represents a group of the formula



where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or (C_1-C_6)-alkylene-R^4,

R^3 represents 1,3-benzodioxole, 2,2-difluoro-1,3-benzodioxole, 2,3-dihydro-1,4-benzodioxin, 2,2,4,4-tetrafluoro-4H-1,3-benzodioxin, phenyl, 5- or 6-membered heteroaryl or (C_5-C_6)-cycloalkyl,

where phenyl, heteroaryl or cycloalkyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of halogen, cyano, trichloromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 represents hydrogen, phenyl, 5- or 6-membered heteroaryl, (C_5-C_6)-cycloalkyl, 5- or 6-membered heterocyclyl, (C_1-C_4)-alkoxy or (C_1-C_4)-alkylamino,

where phenyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of halogen, cyano, trichloromethyl, trifluoromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

and their salts, their solvates and the solvates of their salts.

Very particular preference is given to compounds of the formula (I),

in which

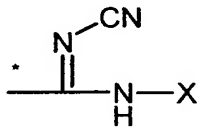
E represents methylene,

m represents 1,

n represents 1,

R^1 represents halogen,

R^2 represents a group of the formula



where

* represents the point of attachment to the pyrazoline ring,

X represents R^3 or (C_1-C_6)-alkylene-R^4,

R^3 represents phenyl, 5- or 6-membered heteroaryl or (C_5-C_6)-cycloalkyl,

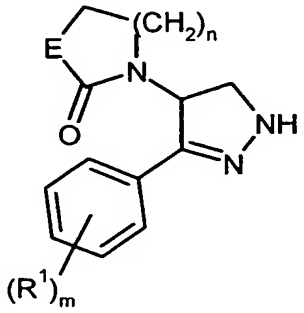
where phenyl, heteroaryl or cycloalkyl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of halogen, cyano, trichloromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 represents hydrogen, phenyl, 5- or 6-membered heteroaryl, (C_5-C_6)-cycloalkyl or 5- or 6-membered heterocyclyl,

where phenyl, heteroaryl, cycloalkyl or heterocyclyl may be substituted by 1 or 2 substituents independently of one another selected from the group consisting of halogen, cyano, trichloromethyl, monofluoromethoxy, difluoromethoxy, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

and their salts, their solvates and the solvates of their salts.

The present invention furthermore provides a process for preparing the novel compounds of the formula (I) where compounds of the formula



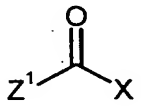
(II),

in which

R^1, E, m and n are as defined above

are reacted either

[A] with compounds of the formula



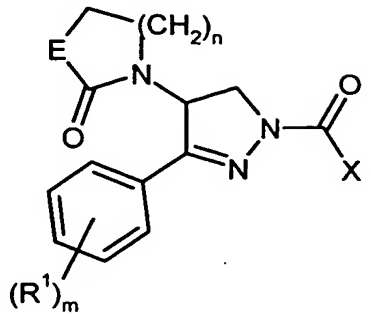
(III),

in which

X is as defined above, and

Z^1 represents halogen, preferably chlorine or bromine, or hydroxyl,

to give compounds of the formula


(Ia),

in which

R^1, E, X, m and n are as defined above,

or

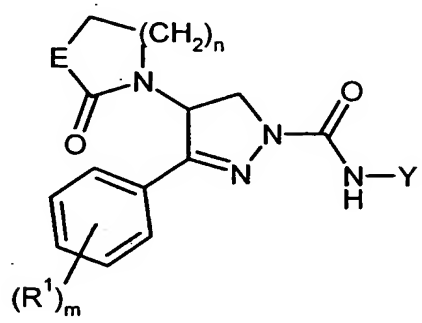
[B] with compounds of the formula

(IV),

in which

Y is as defined above,

to give compounds of the formula


(Ib),

in which

R^1, E, Y, m and n are as defined above,

or

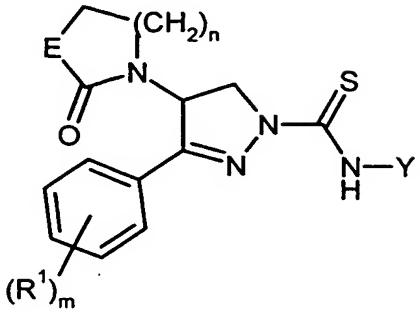
[C] with compounds of the formula

(V),

in which

Y is as defined above,

to give compounds of the formula

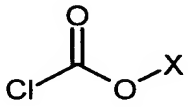

(Ic),

in which

R^1, E, Y, m and n are as defined above,

or

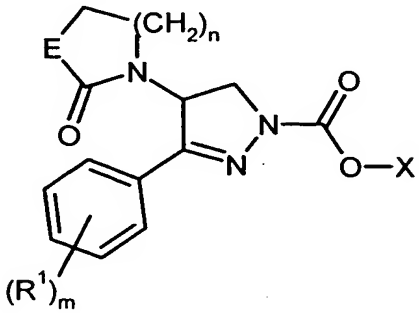
[D] with compounds of the formula


(VI),

in which

X is as defined above,

to give compounds of the formula


(Id),

in which

R^1, E, X, m and n are as defined above,

or

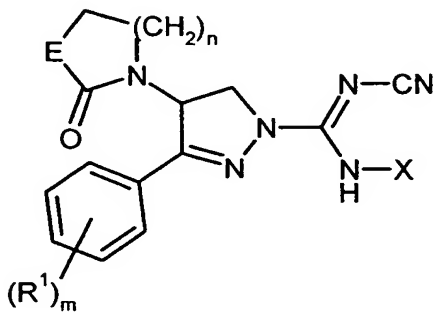
[E] in two steps first with diphenylcyanocarboimidate and then with compounds of the formula

$$X—NH_2 \quad (VII),$$

in which

X is as defined above,

to give compounds of the formula



(Ie),

in which

R^1, E, X, m and n are as defined above.

The general formula (I) encompasses the compounds of the formulae (Ia), (Ib), (Ic), (Id) and (Ie).

The reaction according to process [A] (Z^1 = halogen), process [B], process [C] and process [D] is generally carried out in inert solvents, if appropriate in the presence of a base, preferably in a temperature range of from 0°C to 40°C at atmospheric pressure.

Inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride, trichloromethane or 1,2-dichlorethane, ethers, such as dioxane, tetrahydrofuran or 1,2-dimethoxy-ethane, or other solvents, such as acetone, dimethylformamide, dimethylacetamide, 2-butanone or acetonitrile; preference is given to tetrahydrofuran or methylene chloride.

Bases are, for example, alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or sodium methoxide or potassium methoxide, or sodium ethoxide or potassium ethoxide or potassium *tert*-butoxide, or amides, such as sodium amide, lithium

bis(trimethylsilyl)amide or lithium diisopropylamide, or other bases, such as sodium hydride, DBU, triethylamine or diisopropylethylamine, preference is given to diisopropylethylamine or triethylamine.

The reaction according to process [A] (Z^1 = hydroxyl) is generally carried out in inert solvents, in the presence of dehydrating agents, if appropriate in the presence of a base, preferably in a temperature range of from -70°C to 40°C at atmospheric pressure.

Suitable dehydrating agents are, for example, carbodiimides, such as, for example, *N,N'*-diethyl-, *N,N'*-dipropyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexylcarbodiimide, *N*-(3-dimethylaminoisopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), *N*-cyclohexylcarbodiimide-*N'*-propyloxymethyl-polystyrene (PS-carbodiimide), or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulphate or 2-*tert*-butyl-5-methylisoxazolium perchlorate, or acylamino compounds, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium hexafluorophosphate, or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), or mixtures of these, with bases.

Bases are, for example, alkali metal carbonates, such as, for example, sodium carbonate or potassium carbonate, or sodium bicarbonate or potassium bicarbonate, or organic bases, such as trialkylamines, for example triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine, or DBU, DBN, pyridine, or mixtures of the bases; preference is given to a mixture of 4-dimethylaminopyridine and *N*-methylmorpholine.

The condensation is preferably carried out using *N*-(3-dimethylaminoisopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt), 4-dimethylaminopyridine and *N*-methylmorpholine.

Inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl-*tert*-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl

sulphoxide, acetonitrile or pyridine, in the case of water-miscible solvents also mixtures of the same with water; preference is given to dimethylformamide.

The reaction according to process [E] is preferably carried out in two steps:

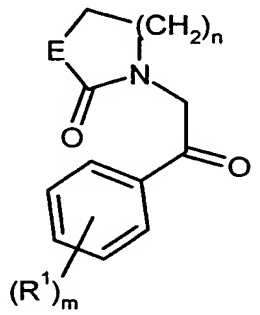
The reaction in the first step is generally carried out in inert solvents, preferably in a temperature range of from 50°C to reflux of the solvent at atmospheric pressure.

Inert solvents are, for example, alcohols, such as methanol, ethanol, *n*-propanol or isopropanol, preference is given to *iso*propanol.

The reaction in the second step is generally carried out in inert solvents, preferably in a temperature range of from 50°C to reflux of the solvent at atmospheric pressure.

Inert solvents are, for example, alcohols, such as methanol, ethanol, *n*-propanol or isopropanol, preference is given to ethanol.

The compounds of the formula (II) are known and/or can be prepared by reacting compounds of the formula



(VIII),

in which

R^1, E, m and n are as defined above,

in a two-step process first with formaldehyde and then with hydrazine hydrate.

The reaction in the first step is generally carried out in inert solvents, in the presence of a base, preferably in a temperature range of from room temperture to reflux of the solvent at atmospheric pressure.

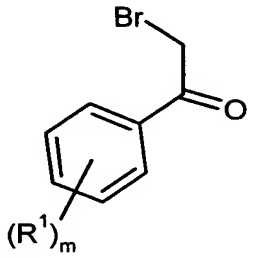
Inert solvents are, for example, alcohols, such as methanol, ethanol, *n*-propanol or isopropanol, preference is given to ethanol.

Bases are, for example, organic bases, such as amine bases, for example piperidine, triethylamine, diisopropylethylamine or DBU, preference is given to piperidine.

The reaction in the second step is generally carried out in inert solvents, preferably in a temperature range of from room temperature to reflux of the solvent at atmospheric pressure.

Inert solvents are, for example, alcohols, such as methanol, ethanol, *n*-propanol or isopropanol, preference is given to ethanol.

The compounds of the formula (VIII) are known and/or can be prepared by reacting compounds of the formula

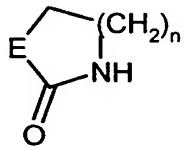


(IX),

in which

R^1 and m are as defined above,

with compounds of the formula



(X),

in which

E and n are as defined above.

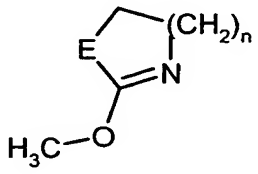
The reaction is generally carried out in inert solvents, if appropriate in the presence of a base, if appropriate with added potassium iodide, preferably in a temperature range of from room temperature to reflux of the solvent at atmospheric pressure.

Inert solvents are, for example, ethers, such as diethyl ether, methyl *tert*-butyl ether, 1,2-dimethoxyethane, dioxane or tetrahydrofuran, hydrocarbons, such as benzene, xylene, toluene, hexane or cyclohexane, or other solvents, such as ethyl acetate, dimethylformamide,

dimethylacetamide, dimethyl sulphoxide, acetonitrile or pyridine, preference is given to dimethylformamide or tetrahydrofuran.

Bases are, for example, alkali metal hydroxides, such as sodium hydroxide, potassium hydroxide or lithium hydroxide, or alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or sodium methoxide or potassium methoxide, or sodium ethoxide or potassium ethoxide or potassium *tert*-butoxide, or amides, such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or other bases, such as sodium hydride, pyridine or DBU; preference is given to sodium hydride.

In an alternative process, under identical reaction conditions, it is also possible to react, instead of compounds of the formula (X), compounds of the formula



(XI),

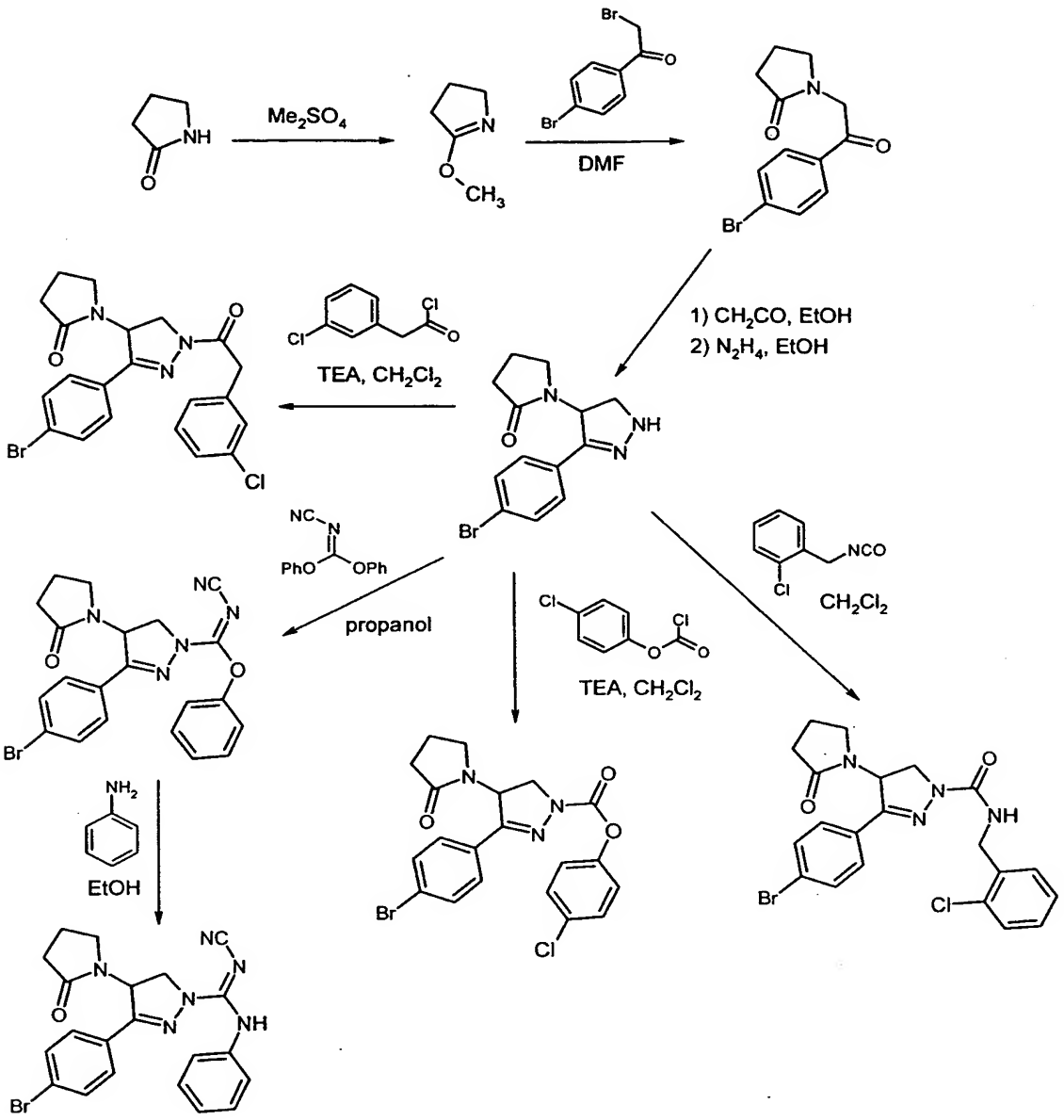
in which

E and n are as defined above.

The compounds of the formulae (III), (IV), (V), (VI), (VII), (IX) and (X) are known or can be synthesized by known processes from the corresponding starting materials.

The preparation of the compounds of the formula (I) can be illustrated by the synthesis scheme below.

Scheme 1:



The compounds according to the invention have an unforeseeable useful pharmacological and pharmacokinetic activity spectrum. They are PAR-1 antagonists.

Accordingly, they are suitable for use as medicaments for the treatment and/or prophylaxis of diseases in humans and animals.

The present invention furthermore provides the use of the compounds according to the invention for the treatment and/or prophylaxis of disorders, preferably cardiovascular disorders, for example thromboembolic disorders and/or thrombotic complications.

For the purpose of the present invention, these include, in particular, myocardial infarction, stable angina pectoris, unstable angina pectoris, stroke, such as, for example, thrombotic stroke and thromoembolic stroke, transitory ischaemic attacks, reocclusion and restenosis after coronary interventions (reocclusion and restenosis after percutaneous coronary interventions, reocclusion and restenosis after coronary bypass operations), disseminated intravasal coagulation, deep vein thromboses and thromboembolism.

The compounds according to the invention can furthermore be used for supporting thrombolytic therapy, for modulating wound healing, for the prevention and treatment of atherosclerotic vascular disorders, such as, for example, restenosis, coronary heart diseases, cerebral ischaemias and peripheral arterial occlusive diseases, of myocardial insufficiency, of hypertension, of inflammable disorders, such as, for example, asthma, inflammable lung disorders, glomerulonephritis, inflammable disorders of the intenstine and rheumatic disorders of the locomotor apparatus, of degenerative disorders, such as, for example, neurodegenerative disorders and osteoporosis, and of neoplastic disorders, such as, for example, cancer.

The present invention furthermore provides the use of the compounds according to the invention for the treatment and/or prophylaxis of disorders, in particular the disorders mentioned above.

The present invention furthermore provides the use of the compounds according to the invention for preparing a medicament for the treatment and/or prophylaxis of disorders, in particular the disorders mentioned above.

The present invention furthermore provides a method for the treatment and/or prophylaxis of disorders, in particular the disorders mentioned above, using a therapeutically effective amount of a compound according to the invention.

The present invention furthermore provides medicaments comprising a compound according to the invention and one or more further active compounds.

The active compound, i.e. the compound according to the invention, can act systemically and/or locally. For this purpose, it can be administered in a suitable way, such as, for example, by the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, transdermal, conjunctival, otic route, or as implant or stent.

For these administration routes, it is possible to administer the active compound in suitable administration forms.

Suitable for oral administration are administration forms which work as described in the prior art and deliver the compounds according to the invention rapidly and/or in modified form, which comprise the compounds according to the invention in crystalline and/or amorphous and/or dissolved form, such as, for example, tablets (uncoated and coated tablets, for example tablets provided with enteric coatings or coatings whose dissolution is delayed or which are insoluble and which control the release of the compounds according to the invention), tablets which rapidly decompose in the oral cavity, or films/wafers, capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of absorption (intramuscularly, subcutaneously, intracutaneously, percutaneously, or intraperitoneally). Administration forms suitable for parental administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Preference is given to oral administration.

Examples suitable for other administration routes are pharmaceutical forms for inhalation (inter alia powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets to be administered lingually, sublingually or buccally, or capsules, suppositories, preparations for the eyes or ears, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milk, pastes, dusting powders, stents or implants.

The compounds according to the invention can be converted into the stated administration forms in a manner known per se. This can take place using inert nontoxic pharmaceutically acceptable auxiliaries. These include, inter alia, carriers (for example microcrystalline cellulose), solvents (for example liquid polyethylene glycols), emulsifiers (for example sodium dodecyl sulphate), dispersants (for example polyvinylpyrrolidone), synthetic and natural biopolymers (for example albumin), stabilizers (for example antioxidants, such as ascorbic acid), colorants (for example inorganic pigments, such as iron oxides) or flavour- and/or odour-masking agents.

The present invention furthermore provides medicaments comprising at least one compound according to the invention, preferably together with one or more inert nontoxic pharmaceutically acceptable auxiliaries, and their use for the purposes mentioned above.

In general, it has been found to be advantageous to administer, in the case of parenteral administration, amounts of about 5 to 250 mg per 24 hours to obtain effective results. In the case of oral administration, the amount is from about 5 to 100 mg per 24 hours.

It may nevertheless be necessary, where appropriate, to deviate from the amounts mentioned, depending on the body weight, the administration route, the individual response to the active compound, the mode of preparation and the time or interval over which administration takes place.

The percentages in the tests and examples below are, unless indicated otherwise, percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and stated concentrations of liquid/liquid solutions are in each case based on volume. The term "w/v" means "weight/volume". Thus, for example, "10% w/v" means: 100 ml of solution or suspension comprise 10 g of substance.

A) **Examples**

Abbreviations:

Boc	*tert*-butoxycarbonyl
$CDCl_3$	deuterated chloroform
CO_2	carbon dioxde
d	day
DIEA	*N,N*-diisopropylethylamine
DMAP	4-*N,N*-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
EDC	*N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide x HCl
eq.	equivalent
ESI	electrospray ionization (in MS)
sat.	saturated
h	hour
HOBt	1-hydroxy-1H-benzotriazole x H_2O
HPLC	high pressure, high performance liquid chromatography
conc.	concentrated
LC-MS	liquid chromatography-coupled mass spectroscopy
min	minutes
MS	mass spectroscopy
MW	molecular weight [g/mol]
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance spectroscopy
R_f	retention index (in TLC)
RP-HPLC	reverse phase HPLC
RT	room temperature
R_t	retention time (in HPLC)
TEA	triethylamine
THF	tetrahydrofuran

HPLC and LC-MS methods:

Method 1 (HPLC): Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm x 2 mm, 3.5 µm; mobile phase A: 5 ml of $HClO_4$/l of water, mobile phase B: acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 6.5 min 90% B; flow rate: 0.75 ml/min, temp.: 30°C, UV detection: 210 nm.

Method 2 (LC-MS): Instrument: Micromass Quattro LCZ, with HPLC Agilent Series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; mobile phase A: 1 l of water + 1 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 1 ml of 50% strength formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10%A; oven: 55°C, flow rate: 0.8 ml/min, UV detection: 208-400 nm.

Method 3 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 Series; UV DAD; column: Grom-Sil 120 ODS-4 HE 50 mm x 2 mm, 3.0 µm; mobile phase A: water + 500 µl of 50% strength formic acid / l, mobile phase B: acetonitrile + 500 µl of 50% strength formic acid / l; gradient: 0.0 min 0% B → 2.9 min 70% B → 3.1 min 90% B → 4.5 min 90% B; oven: 50°C, flow rate: 0.8 ml/min, UV detection: 210 nm.

Method 4 (LC-MS): MS instrument: Micromass TOF (LCT); HPLC instrument: 2-column setup, Waters2690; column: YMC-ODS-AQ, 50 mm x 4.6 mm, 3.0 µm; mobile phase A: water + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid; gradient: 0.0 min 100% A → 0.2 min 95% A → 1.8 min 25% A → 1.9 min 10% A → 2.0 min 5% A → 3.2 min 5% A; oven: 40°C; flow rate: 3.0 ml/min; UV detection: 210 nm.

Method 5 (LC-MS): Instrument: Micromass Platform LCZ with HPLC Agilent Series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; mobile phase A: 1 l of water + 1 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 1 ml of 50% strength formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 4.5 min 10% A; oven: 55°C, flow rate: 0.8 ml/min, UV detection: 210 nm.

Method 6 (HPLC): Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm x 2 mm, 3.5 µm; mobile phase A: 5 ml of $HClO_4$/l of water, mobile phase B: acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 15 min 90% B; flow rate: 0.75 ml/min, temp.: 30°C, UV detection: 210 nm.

Method 7 (GC-MS): Instrument: Micromass GCT, GC6890; column: Restek RTX-35MS, 30 m x 250 µm x 0.25 µm; constant flow with helium: 0.88 ml/min; oven: 60°C; inlet: 250°C; gradient:

60°C (maintained for 0.30 min), 50°C/min → 120°C, 16°C/min → 250°C, 30°C/min → 300°C (maintained for 1.7 min).

Method 8 (HPLC, separation of enantiomers): chiral silica gel selector KBD 6136 (10 µm, 350x30mm) based on the selector poly(*N*-methacryloyl-L-leucine-l-menthylamide); mobile phase: *tert*-butyl methyl ether/ethyl acetate 90/10; temperature: 24°C; flow rate: 50 ml/min; UV detection: 254 nm.

Method 9 (HPLC): chiral silica gel selector KBD 8361A (250 x 4.6 mm) based on the selector poly(*N*-methacryloyl-L-leucine-l-menthylamide); mobile phase: *tert*-butyl methyl ether/ethyl acetate 40/10; temperature: 24°C; flow rate: 1 ml/min; UV detection: 254 nm.

Method 10 (HPLC, separation of enantiomers): chiral silica gel selector KBD 8361A (250 x 20 mm) based on the selector poly(*N*-methacryloyl-L-leucine-l-menthylamide); *iso*hexane/ethyl acetate 20/10; temperature: 24°C; flow rate: 25 ml/min; UV detection: 254 nm.

Method 11 (HPLC): analytical HPLC: chiral silica gel selector KBD 8361A (250 x 4.6 mm) based on the selector poly(*N*-methacryloyl-L-leucine-l-menthylamide); isohexane/ethyl acetate 3/7; temperature: 24°C; flow rate: 1 ml/min; UV detection: 254 nm.

Methode 12 (HPLC, separation of enantiomers): column: Chiralcel OD (250 x 20 mm); methanol/isopropanol 1/1; temperature: 24°C; flow rate: 20 ml/min; UV detection: 254 nm.

Method 13 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 Series; UV DAD; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water + 0.5 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50 strength formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min. 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 14 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2795; column: Phenomenex Synergi 2 µ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water + 0.5 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.5 min 5% A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 15 (LC-MS): Instrument: Micromass Quattro LCZ with HPLC Agilent Series 1100; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water

+ 0.5 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.5 min 5% A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 208-400 nm.

Method 16 (LC-MS): Instrument: Micromass Platform LCZ with HPLC Agilent Series 1100; column: Phenomenex Synergi 2 µ Hydro-RP Mercury 20 mm x 4 mm; mobile phase A: 1 l of water + 0.5 ml of 50% strength formic acid, mobile phase B: 1 l of acetonitrile + 0.5 ml of 50% strength formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.5 min 5% A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

Method 17 (HPLC, separation of diastereomers/enantiomers): chiral selector Chiralpak AD-H (250 mm x 20 mm); isohexane/ethanol 55:45 (vol/vol); temperature: 25°C; flow rate: 15 ml/min; UV detection: 220 nm.

Method 18 (HPLC, separation of enantiomers): chiral silica gel selector KBD 5326 (250 mm x 20 mm) based on the selector poly(*N*-methacryloyl-L-leucine-l-menthylamide); ethyl acetate; temperature: 24°C; flow rate: 25 ml/min; UV detection: 254 nm.

Method 19 (HPLC, separation of enantiomers): chiral silica gel selector KBD 5326 (250 mm x 20 mm) based on the selector poly(*N*-methacryloyl-L-leucinedicyclopropylmethylamide); acetic acid; temperature: 24°C; flow rate: 25 ml/min; UV detection: 260 nm.

Method 20 (HPLC, separation of enantiomers): chiral silica gel selector KBD 5326 (250 mm x 20 mm) based on the selector poly(*N*-methacryloyl-L-leucinedicyclopropylmethylamide); acetic acid; temperature: 24°C; flow rate: 25 ml/min; UV detection: 280 nm.

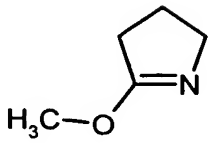
Method 21 (HPLC, separation of enantiomers): chiral selector Daicel Chiralcel OD-H (250 mm x 20 mm); isohexane/ethanol 40:60 (vol/vol); temperature: 40°C; flow rate: 15 ml/min; UV detection: 220 nm.

Method 22 (HPLC, separation of enantiomers): chiral selector Daicel Chiralcel OD-H (250 mm x 20 mm); isohexane/ethanol 50:50 (vol/vol); temperature: 25°C; flow rate: 15 ml/min; UV detection: 220 nm.

Starting materials:

Example I

5-Methoxy-3,4-dihydro-2*H*-pyrrole



20 g (235 mmol) of pyrrolidin-2-one are added to 22.2 ml (235 mmol) of dimethyl sulphate, and the resulting mixture is stirred at 60°C for 16 h. After cooling, the mixture is added to 200 ml of sat. aqueous potassium carbonate solution and stirred for 30 min. The mixture is extracted three times with diethyl ether, and the combined organic phases are dried over sodium sulphate. Removal of the solvent is followed by distillative purification (70 mbar). This gives 10.2 g (44% of theory) of the desired product.

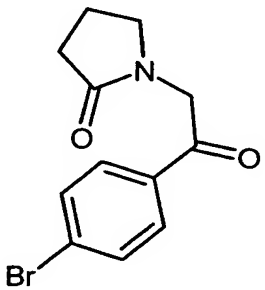
GC-MS (method 7): R_t = 2.57 min

MS (ESIpos): m/z = 99 $(M+H)^+$

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.95-2.12 (m, 2H), 2.46 (dd, 2H), 3.66 (tt, 2H), 3.81 (s, 3H) ppm.

Example II

1-[2-(4-Bromophenyl)-2-oxoethyl]pyrrolidin-2-one



11.3 g (114 mmol) of 5-methoxy-3,4-dihydro-2*H*-pyrrole are added to a solution of 26.4 g (94.9 mmol) of 2-bromo-1-(4-bromophenyl)-2-ethanone in 90 ml of DMF, and the mixture is then stirred at 50°C for 24 h. After cooling, the solution is stirred into water and extracted with dichloromethane. The combined organic phases are dried over sodium sulphate and, after

concentration, purified by flash chromatography on silica gel (mobile phase ethyl acetate). This gives 17.2 g (64% of theory) of the desired product.

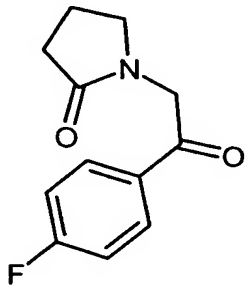
HPLC (method 1): R_t = 3.93 min

MS (ESIpos): m/z = 282 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.12 (dt, 2H), 2.47 (dd, 2H), 3.48 (dd, 2H), 4.66 (s, 2H), 7.62 (d, 2H), 7.83 (d, 2H) ppm.

Example III

1-[2-(4-Fluorophenyl)-2-oxoethyl]pyrrolidin-2-one



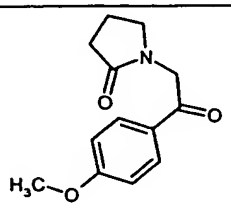
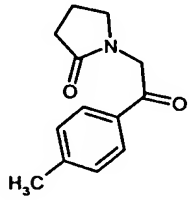
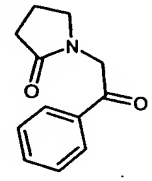
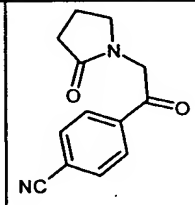
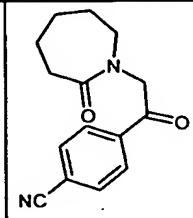
2.19 g (22.1 mmol) of 5-methoxy-3,4-dihydro-2*H*-pyrrole are added to a solution of 4.00 g (18.4 mmol) of 2-bromo-1-(4-fluorophenyl)-2-ethanone in 15 ml of DMF, and the mixture is then stirred at 50°C for 24 h. After cooling, the solution is stirred into water and extracted with dichloromethane. The combined organic phases are dried over sodium sulphate and, after concentration, purified by flash chromatography on silica gel (mobile phase cyclohexane/ethyl acetate 4:1 → ethyl acetate). This gives 3.93 g (90% of theory) of the desired product.

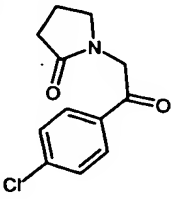
HPLC (method 1): R_t = 3.56 min

MS [DCI (NH_3)]: m/z = 222 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.93-2.07 (m, 2H), 2.30 (dd, 2H), 3.39 (dd, 2H), 4.74 (s, 2H), 7.34-7.44 (m, 2H), 8.03-8.11 (d, 2H) ppm.

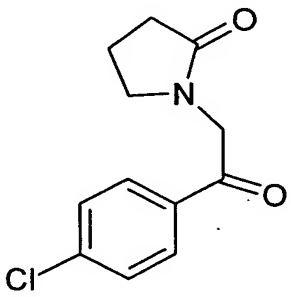
The compounds of Example IV to IX are prepared analogously to Example II.

Example	Structure	Yield	R_t [min] (method)	Mass DCI (NH_3)
IV		37%	3.53 (1)	251 $[M+NH_4]^+$
V		51%	3.77 (1)	235 $[M+NH_4]^+$
VI		74%	3.49 (1)	221 $[M+NH_4]^+$
VII		81%	3.40 (1)	246 $[M+NH_4]^+$
VIII	 Starting material: caprolactam methyl ether	63%	4.25 (1)	310 $[M+H]^+$

Example	Structure	Yield	R_t [min] (method)	Mass DCI (NH_3)
IX		92%	3.81 (1)	255 $[M+NH_4]^+$

Preparation process for Example IX

1-[2-(4-Chlorophenyl)-2-oxoethyl]pyrrolidin-2-one



29.44 g (126.09 mmol) of 4-chlorophenacyl bromide and 15 g (151.31 mmol) of 5-methoxy-3,4-dihydro-2H-pyrrole in 100 ml of dimethylformamide are heated at 50°C overnight. The solution is then poured into 800 ml of water and extracted three times with ethyl acetate. The organic phase is washed with saturated sodium chloride solution and dried over magnesium sulphate. Removal of the solvent under reduced pressure gives 30 g (98% of theory) of product.

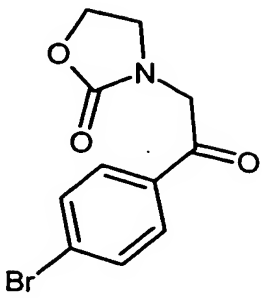
LC-MS (method 14): R_t = 1.65 min,

MS (ESIpos): m/z = 238 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.00 (m, 2H), 2.29 (t, 2H), 3.38 (t, 2H), 4.75 (s, 2H), 7.64 (m, 2H), 7.99 (d, 2H).

Example X

3-[2-(4-Bromophenyl)-2-oxoethyl]-1,3-oxazolidin-2-one



157 mg (1.80 mmol) of 1,3-oxazolidin-2-one are added to a suspension of 79 mg (2.0 mmol) of sodium hydride in 3.6 ml of THF, and the mixture is stirred at RT for 1 h. 60 mg (0.36 mmol) of potassium iodide and a solution of 500 mg (1.80 mmol) of 2-bromo-1-(4-bromophenyl)-2-ethanone in 3.6 ml of THF are added, and the mixture is then stirred at 70°C for 20 h. After cooling, 15 ml of water are carefully added, and the mixture is extracted three times with dichloromethane. The combined organic phases are washed with saturated sodium chloride solution and dried over sodium sulphate. After concentration, the residue is purified by flash chromatography on silica gel (mobile phase cyclohexane/ethyl acetate 4:1). This gives 49 mg (8% of theory) of the desired product.

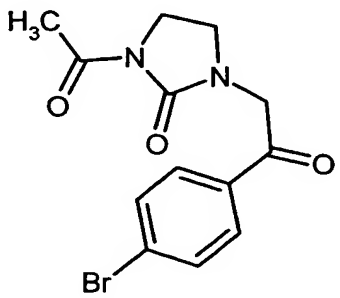
HPLC (method 1): R_t = 3.94 min

MS [DCI (NH_3)]: m/z = 301 $(M+NH_4)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.55 (t, 2H), 3.93 (t, 2H), 4.66 (s, 2H), 7.63-7.68 (m, 2H), 7.81-7.85 (m, 2H) ppm.

Example XI

1-Acetyl-3-[2-(4-bromophenyl)-2-oxoethyl]imidazolidin-2-one



230 mg (1.80 mmol) of 1-acetylimidazolidin-2-one are added to a suspension of 79 mg (2.0 mmol) sodium hydride in 4 ml of THF and the mixture is stirred at RT for 1 h. The mixture is diluted with 4 ml of THF, and the suspension is added to a mixture of 60 mg (0.36 mmol) of potassium iodide

and 500 mg (1.80 mmol) of 2-bromo-1-(4-bromophenyl)-2-ethanone in 4 ml of THF. The mixture is then stirred at 70°C for 20 h. After cooling, 15 ml of water are carefully added and the mixture is extracted three times with dichloromethane. The combined organic phases are washed with saturated sodium chloride solution and dried over sodium sulphate. After concentration, the mixture is purified by flash chromatography on silica gel (mobile phase dichloromethane/ethanol 100:1). This gives 139 mg (24% of theory) of the desired product.

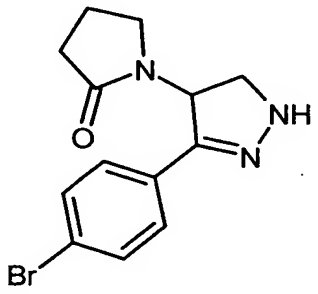
HPLC (method 1): R_t = 4.05 min

MS (ESIpos): m/z = 325 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 3.73 (dd, 2H), 4.44 (dd, 2H), 4.67 (s, 2H), 7.62-7.67 (m, 2H), 7.79-7.86 (m, 2H) ppm.

Example XII

1-[3-(4-Bromophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one



2.46 ml (24.8 mmol) of piperidine are added dropwise to a solution of 4.67 g (16.6 mmol) of 1-[2-(4-bromophenyl)-2-oxoethyl]pyrrolidin-2-one (Example II) and 2.01 g (24.8 mmol) of formaldehyde in 25 ml of ethanol. The mixture is stirred at RT for 20 h. The resulting precipitate is filtered off, washed with 6 ml of ethanol and dried under reduced pressure. The crude product is suspended in 100 ml of ethanol, and 2.86 g (57.1 mmol) of hydrazine hydrate are added. The suspension is heated under reflux for 1 h. After cooling, the solvent is removed and the residue is triturated with a mixture of 24 ml of diethyl ether and 8 ml of water. The residue is filtered off, washed twice with 3 ml of diethyl ether and then dried under reduced pressure. This gives 3.70 g (73% of theory) of the desired product.

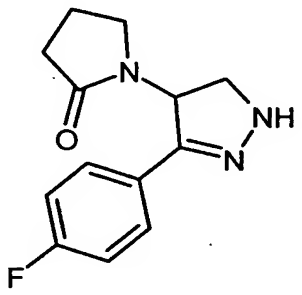
HPLC (method 1): R_t = 3.69 min

MS (ESIpos): m/z = 308 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.78-2.05 (m, 2H), 2.29-2.40 (m, 2H), 2.98 (ddd, 1H), 3.38 (ddd, 1H), 3.49 (dd, 1H), 3.66 (dd, 1H), 5.87 (dd, 1H), 7.46-7.52 (m, 2H), 7.55-7.62 (m, 2H) ppm.

Example XIII

1-[3-(4-Fluorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one



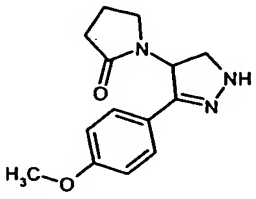
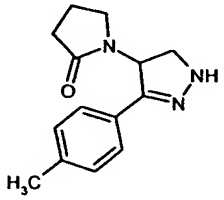
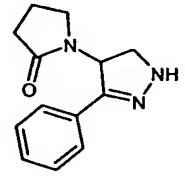
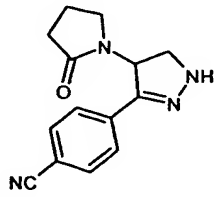
2.62 ml (26.4 mmol) of piperidine are added dropwise to a solution of 3.90 g (17.6 mmol) of 1-[2-(4-fluorophenyl)-2-oxoethyl]pyrrolidin-2-one (Example III) and 2.15 g (26.4 mmol) of formaldehyde in 30 ml ethanol. The mixture is stirred at 70°C for 18 h. The solvent is removed, and the crude product is then suspended in 30 ml of ethanol and 4.49 g (90 mmol) of hydrazine hydrate are added. The suspension is heated under reflux for 1 h. After cooling, the solid is filtered off and washed with methanol. This gives 2.19 g (34% of theory) of the desired product.

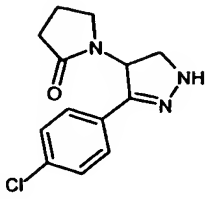
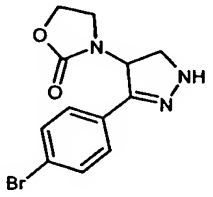
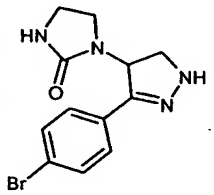
HPLC (method 1): R_t = 3.28 min

MS (ESIpos): m/z = 248 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.76-2.05 (m, 2H), 2.23-2.48 (m, 2H), 3.01 (ddd, 1H), 3.38 (ddd, 1H), 3.48 (dd, 1H), 3.65 (dd, 1H), 5.83 (dd, 1H), 7.01-7.19 (m, 2H), 7.65-7.74 (m, 2H) ppm.

The compounds of Example XIV to XX are prepared analogously to Example XII.

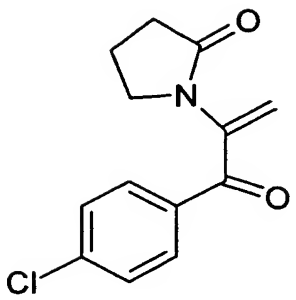
Example	Structure	Yield (Reaction temperature methylenation)	R_t [min] (method)	Mass
XIV		21% (50°C)	3.27 (1)	260 ESIpos $[M+H]^+$
XV		9% (50°C 20h; then 70°C 20h)	3.42 (1)	244 ESIpos $[M+H]^+$
XVI		19% (50°C 20h; then 70°C 20h)	3.18 (1)	230 ESIpos $[M+H]^+$
XVII		50% (RT 48h)	3.35 (1)	255 ESIpos $[M+H]^+$

Example	Structure	Yield (Reaction temperature methylenation)	R_t [min] (method)	Mass
XVIII		67% (RT 48h)	3.61 (1)	264 DCI (NH_3) $[M+H]^+$
XIX		21% (RT 20h)	3.76 (1)	310 ESIpos $[M+H]^+$
XX		24% (RT 20h)	2.18 (2)	311 ESIpos $[M+H]^+$

Preparation process for Example XVIII

1st step

1-[1-(4-Chlorobenzoyl)vinyl]pyrrolidin-2-one



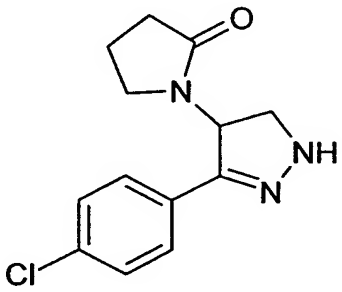
13 g (54.69 mmol) of 1-[2-(4-chlorophenyl)-2-oxoethyl]pyrrolidin-2-one and 6.65 g (82.04 mmol) of 37% formaldehyde are initially charged in 150 ml of ethanol and, with 6.98 g (82.04 mmol) of piperidine, heated at 70°C overnight. After cooling to room temperature, the solvent is removed under reduced pressure and the product is reacted further without further purification.

LC-MS (method 13): R_t = 1.97 min,

MS (ESIpos): m/z = 249 $(M+H)^+$

2nd step

1-[3-(4-Chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one



Under argon, 17.58 g (70.40 mmol) of 1-[1-(4-chlorobenzoyl)vinyl]pyrrolidin-2-one are dissolved in 100 ml of ethanol and, with 12.33 g (246.4 mmol) of hydrazine hydrate, heated at 100°C for one hour. After cooling to room temperature, the precipitated product is filtered off and washed twice with a little ethanol. This gives 7.05 g (44% of theory) of product.

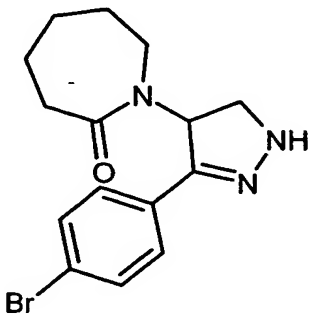
LC-MS (method 13): R_t = 1.72 min,

MS (ESIpos): m/z = 264 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.74 (m, 1H), 1.85 (m, 1H), 2.18 (m, 2H), 2.76 (m, 1H), 3.27 (m, 1H), 3.42 (m, 2H), 5.66 (dd, 1H), 7.43 (m, 2H), 7.55 (d, 2H), 7.61 (m, 1H).

Example XXI

1-[3-(4-Bromophenyl)-4,5-dihydro-1H-pyrazol-4-yl]azepan-2-one



0.67 ml (6.74 mmol) of piperidine is added dropwise to a solution of 1.90 g (6.31 mmol) of 1-[2-(4-bromophenyl)-2-oxoethyl]azepan-2-one (Example VIII) and 0.75 g (9.19 mmol) of formaldehyde in 15 ml ethanol. The mixture is stirred at RT for 23 h and then at 50°C for 44 h. After addition of 0.20 g (2.45 mmol) of formaldehyde, the mixture is stirred at 70°C for 24 h. Concentration under reduced pressure gives 2.63 g of crude product. 0.69 g (2.15 mmol) of the crude product is suspended in 15 ml of ethanol, and 0.38 g (7.52 mmol) of hydrazine hydrate is added. The suspension is heated under reflux for 24 h. After cooling, the solvent is removed and the residue is triturated with 7.5 ml of diethyl ether. The solid is filtered off, washed twice with 3 ml of diethyl ether and then dried under reduced pressure. This gives 0.55 g (71% of theory) of the desired product.

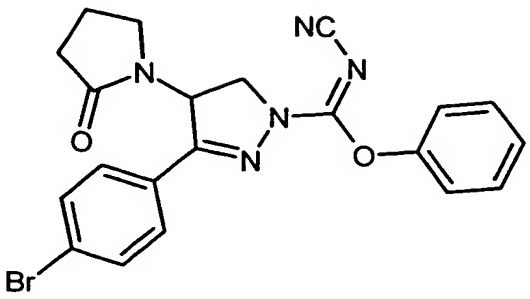
HPLC (method 1): R_t = 3.89 min

MS (ESIpos): m/z = 338 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.39-1.76 (m, 6H), 2.54 (dd, 2H), 3.19 (m_c, 2H), 3.45 (dd, 1H), 3.72 (dd, 1H), 5.85 (br.s, 1H), 6.35 (dd, 1H), 7.45-7.52 (m, 2H), 7.56-7.63 (m, 2H) ppm.

Example XXII

3-(4-Bromophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-phenylimidate



500 mg (1.62 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one (Example XII) are added to a suspension of 387 mg (1.62 mmol) of diphenylcyanocarboimidate in 7.5 ml of 2-propanol. The mixture is heated under reflux for 3 d. After cooling, the precipitate obtained is filtered off with suction and washed with a little diethyl ether. This gives 409 mg (56% of theory) of the desired product.

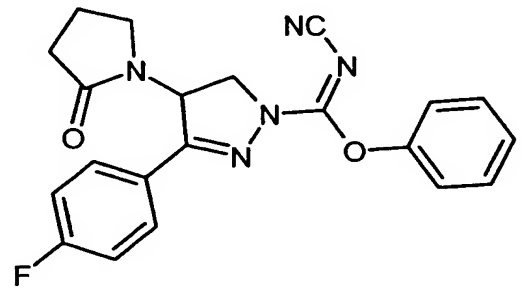
HPLC (method 1): R_t = 4.43 min

MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.83-2.20 (m, 2H), 2.25-2.57 (m, 2H), 3.01 (ddd, 1H), 3.36 (ddd, 1H), 4.19 (dd, 1H), 4.38 (dd, 1H), 6.21 (dd, 1H), 7.10-7.20 (m, 2H), 7.29-7.37 (m, 1H), 7.38-7.50 (m, 2H) 7.52-7.61 (m, 2H), 7.65-7.77 (m, 2H) ppm.

Example XXIII

3-(4-Fluorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-phenylimidate



500 mg (2.02 mmol) of 1-[3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one (Example XIII) are added to a suspension of 482 mg (2.02 mmol) of diphenylcyanocarboimidate in 9 ml of 2-propanol. The mixture is heated under reflux for 3 d. After cooling, the precipitate obtained is filtered off with suction and washed with diethyl ether. This gives 570 mg (72% of theory) of the desired product.

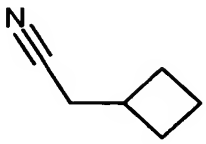
HPLC (method 1): R_t = 4.30 min

MS (ESIpos): m/z = 392 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.88-2.15 (m, 2H), 2.30-2.53 (m, 2H), 3.02 (ddd, 1H), 3.36 (ddd, 1H), 4.20 (dd, 1H), 4.38 (dd, 1H), 6.21 (dd, 1H), 7.08-7.20 (m, 4H), 7.29-7.35 (m, 1H), 7.39-7.48 (m, 2H), 7.82-7.90 (m, 2H) ppm.

Example XXIV

Cyclobutylacetonitrile



181 mg (3.69 mmol) of sodium cyanide and 50 mg (0.34 mmol) of sodium iodide are added to a solution of 500 mg (3.36 mmol) of bromomethylcyclobutane in 4 ml of dimethyl sulphoxide. The mixture is stirred at room temperature for 3 days, saturated sodium chloride solution is then added and the mixture is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated under reduced pressure. 100 mg (31% of theory) of cyclobutylacetonitrile in the form of an oil are obtained as intermediate.

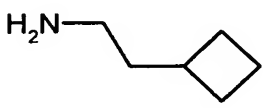
GC-MS (method 7): R_t = 3.14 min.

MS (ESI pos) m/z = 95 $(M)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.65-1.9 (m, 4H), 2.0-2.15 (m, 2H), 2.53-2.64 (m, 3H).

Example XXV

2-Cyclobutylethylamine



Under argon, 3.15 ml (3.15 mmol) of a 1M solution of borane/tetrahydrofuran complex in THF are added to a solution of 100 mg (1.05 mmol) of cyclobutylacetonitrile in 2 ml of absolute THF, and the mixture is stirred at room temperature for 1 h. Methanol is then carefully added, and after 1 h,

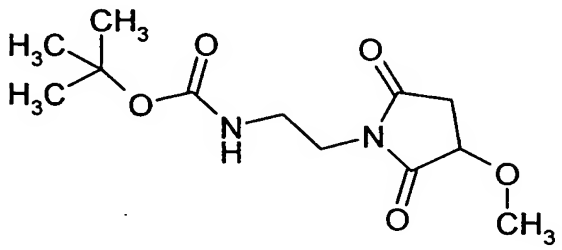
the solution is concentrated under reduced pressure. The product obtained is 120 mg (quant.) of 2-cyclobutylethylamine in the form of an oil which is used without further purification for the next step.

GC-MS (method 7): R_t = 2.73 min.

MS (ESI pos): m/z = 100 $(M+H)^+$

Example XXVI

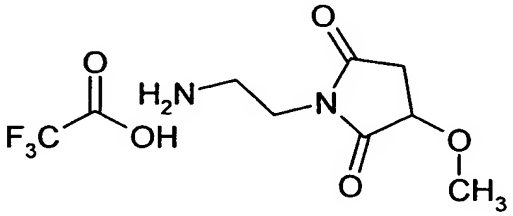
tert-Butyl [2-(3-methoxy-2,5-dioxopyrrolidin-1-yl)ethyl]carbamate



0.123 g (0.769 mmol) of *N*-Boc-ethylenediamine is mixed with 0.1 g (0.769 mmol) of 3-methoxy-dihydrofuran-2,5-dione and slowly heated to 160°C. The temperature is maintained for two hours. After cooling to room temperature, the product is, without further purification, converted into 1-(2-aminoethyl)-3-methoxypyrrolidin-2,5-dione trifluoracetate.

Example XXVII

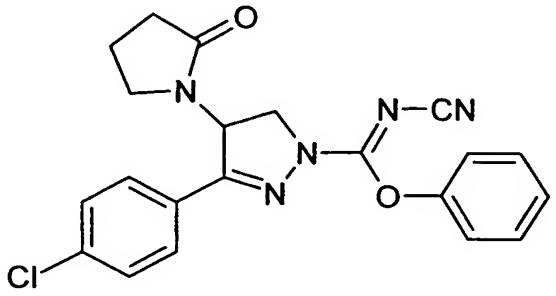
1-(2-Aminoethyl)-3-methoxypyrrolidine-2,5-dione trifluoracetate



1 ml trifluoroacetic acid is added to 0.21 g (0.77 mmol) of *tert*-butyl [2-(3-methoxy-2,5-dioxopyrrolidin-1-yl)ethyl]carbamate in 5 ml of tetrahydrofuran, and the mixture is stirred for 30 min. The solvent is removed under reduced pressure and the product is, without further purification, convered into Example 414.

Example XXVIII

Phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)- 4,5-dihydro-1H-pyrazole-1-carboximidoate



Under argon, 10 g (37.91 mmol) of 1-[3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one and 9 g (37.91 mmol) of diphenylcyanocarboimidate in 180 ml of 2-propanol are heated at reflux overnight. After cooling to room temperature, the resulting precipitate is filtered off and washed repeatedly with diethyl ether. This gives 10.85 g (70% of theory) of the product.

LC-MS (method 15): R_t = 2.29 min,

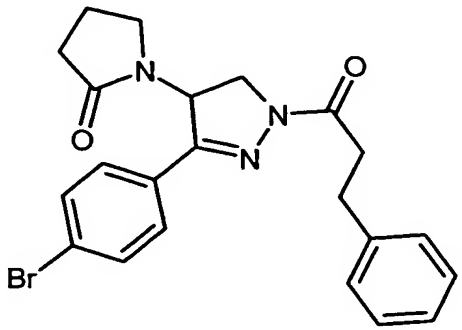
MS (ESI pos): m/z = 408 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.85 (m, 2H), 2.24 (m, 2H), 2.80 (m, 1H), 3.49 (m, 1H), 4.44 (m, 2H), 6.10 (dd, 1H), 7.31 (m, 3H), 7.47 (d, 2H), 7.62 (m, 2H), 7.71 (m, 2H).

Working Examples:

Example 1

1-[3-(4-Bromophenyl)-1-(3-phenylpropionyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one



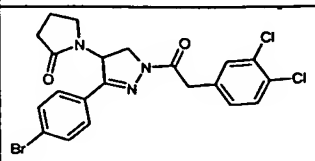
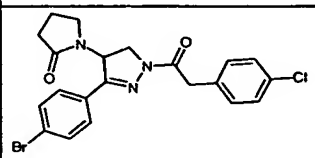
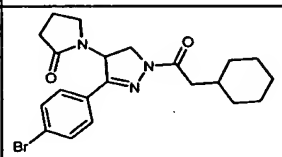
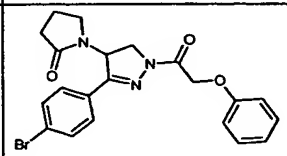
At RT, a mixture of 77.1 mg (0.25 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XII) and 0.04 ml (0.30 mmol) of TEA in 2 ml of dichloromethane is added to 50.6 mg (0.30 mmol) of 3-phenylpropionyl chloride. The solution is stirred at RT for 18 h. After concentration, the residue is stirred with 1 ml of warm dimethyl sulphoxide and 0.4 ml of warm methanol. The mixture is filtered off with suction through a silica gel cartridge, and the residue that remains is washed with diethyl ether. This gives 79.2 mg (72% of theory) of product.

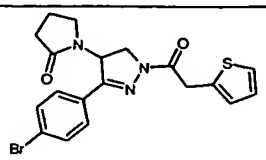
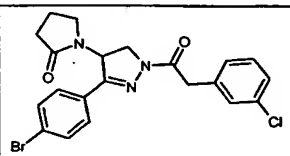
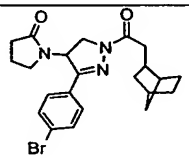
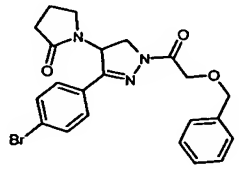
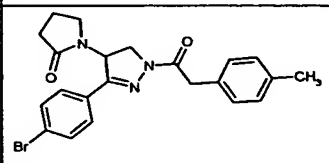
HPLC (method 1): R_t = 4.90 min

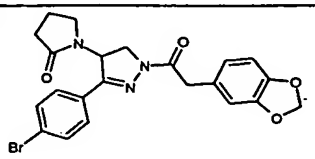
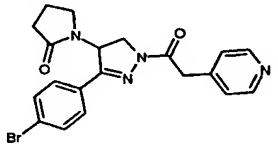
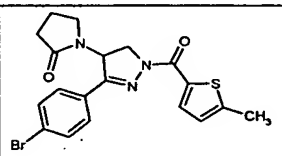
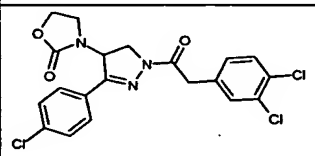
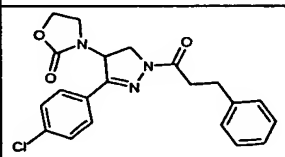
MS [DCI (NH_3]: m/z = 440 $(M+H)^+$

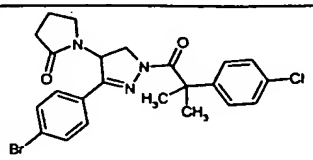
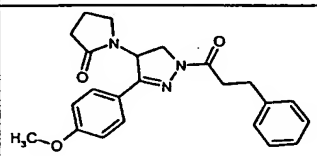
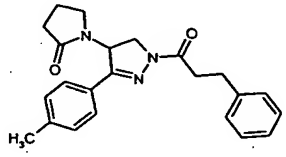
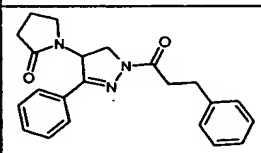
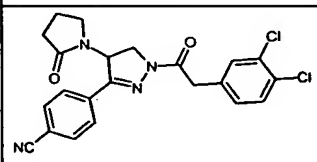
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.73-2.08 (m, 2H), 2.20-2.47 (m, 2H), 2.65-2.78 (m, 1H), 2.99-3.22 (m, 5H), 3.90-4.09 (m, 2H), 6.01 (dd, 1H), 7.14-7.31 (m, 5H), 7.49-7.65 (m, 4H) ppm.

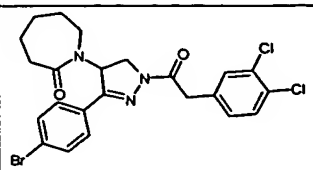
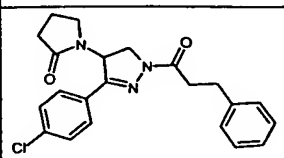
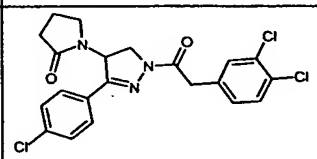
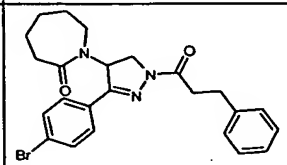
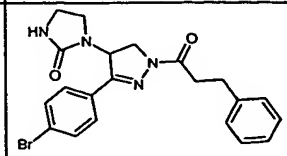
The compounds of Examples 2 to 25 are prepared analogously to Example 1. The crude products from the reactions are purified by trituration and/or by preparation HPLC.

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
2		70% (2h)	5.17 (1)	513 DCI (NH_3) $[M+NH_4]^+$
3		53% (2h)	4.97 (1)	477 DCI (NH_3) $[M+NH_4]^+$
4		87% (18h)	5.25 (1)	449 DCI (NH_3) $[M+NH_4]^+$
5		66% (2h)	4.80 (1)	459 DCI (NH_3) $[M+NH_4]^+$

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
6		35% (2h)	4.76 (1)	449 DCI (NH_3) $[M+NH_4]^+$
7		62% (2h)	5.05 (1)	477 DCI (NH_3) $[M+NH_4]^+$
8		79% (2h)	5.33 (1)	444 DCI (NH_3) $[M+H]^+$
9		79% (2h)	4.75 (1)	473 DCI (NH_3) $[M+NH_4]^+$
10		26% (2h)	4.99 (1)	457 DCI (NH_3) $[M+NH_4]^+$

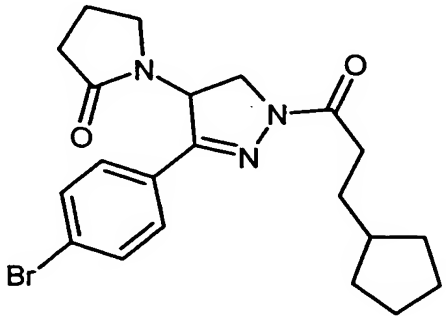
Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
11		59% (2h)	4.70 (1)	487 DCI (NH_3) $[M+NH_4]^+$
12		49% (18h)	3.82 (1)	427 ESIpos $[M+H]^+$
13		62% (18h)	4.86 (1)	432 ESIpos $[M+H]^+$
14		39% (18h)	5.17 (1)	453 ESIpos $[M+H]^+$
15		47% (18h)	4.88 (1)	398 ESIpos $[M+H]^+$

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
16		63% (18h)	5.13 (1)	505 DCI (NH_3) $[M+NH_4]^+$
17		5% (18h)	3.55 (5)	392 ESIpos $[M+H]^+$
18		7% (2h)	3.70 (5)	376 ESIpos $[M+H]^+$
19		23% (2h)	4.61 (1)	362 ESIpos $[M+H]^+$
20		12% (48h)	4.76 (1)	458 DCI (NH_3) $[M+NH_4]^+$

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
21		79% (48h)	5.45 (1)	524 ESIpos $[M+H]^+$
22		56% (48h)	4.84 (1)	396 ESIpos $[M+H]^+$
23		49% (48h)	5.14 (1)	467 ESIpos $[M+NH_4]^+$
24		50% (48h)	5.17 (1)	468 ESIpos $[M+H]^+$
25		7% (4h)	4.63 (1)	441 DCI (NH_3) $[M+NH_4]^+$

Example 26

1-[3-(4-Bromophenyl)-1-(3-cyclopentylpropionyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one



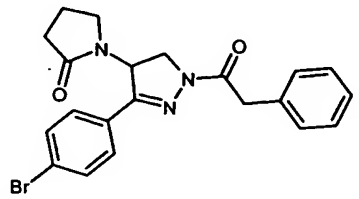
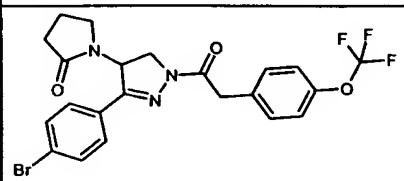
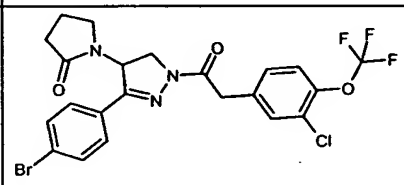
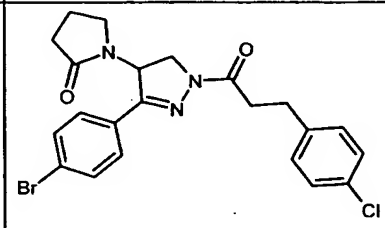
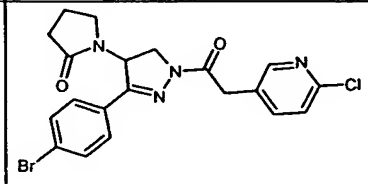
As a suspension in 0.5 ml of DMF, 19.6 mg (0.15 mmol) of HOBt, 55.6 mg (0.29 mmol) of EDC and 1 mg (0.01 mmol) of DMAP are added to 24.7 mg (0.17 mmol) of 3-cyclopentylcarboxylic acid. After 5 min, a suspension of 0.06 ml (0.58 mmol) of *N*-methylmorpholine and 44.7 mg (0.15 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XII) is added, and the mixture is kept at RT for 18 h. Preparation HPLC (Grom-Sil RP18; mobile phase acetonitrile-water/0.3% formic acid gradient 10:90 -> 90:10) gives 17.3 mg (28% of theory) of product.

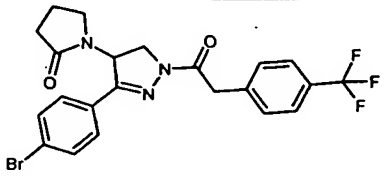
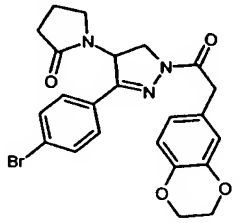
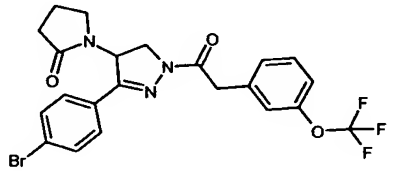
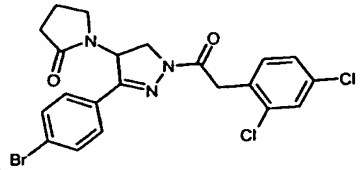
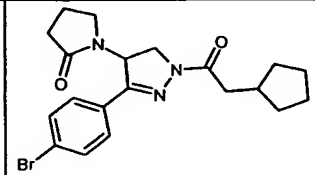
HPLC (method 1): R_t = 5.19 min

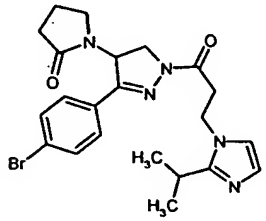
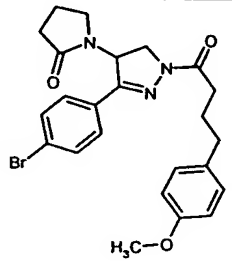
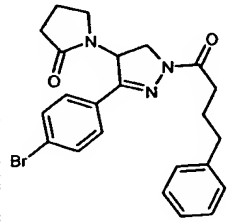
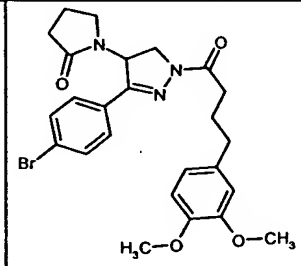
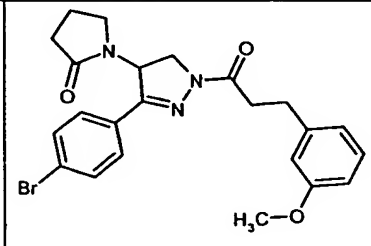
MS [DCI (NH_3)]: m/z = 432 $(M+H)^+$

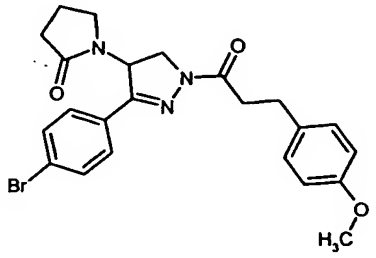
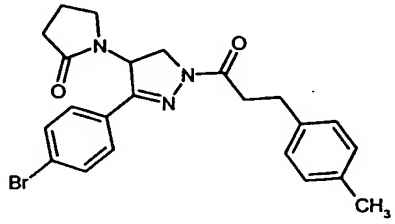
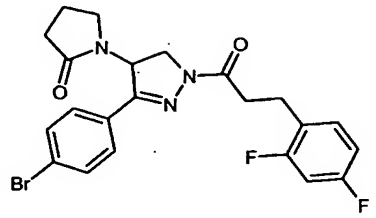
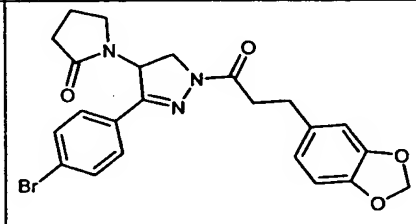
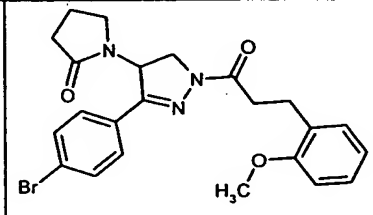
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.05-1.28 (m, 2H), 1.41-2.07 (m, 11H), 2.38 (ddd, 2H), 2.72-2.94 (m, 3H), 3.22 (ddd, 1H), 3.93-4.09 (m, 2H), 6.04 (dd, 1H), 7.49-7.68 (m, 4H) ppm.

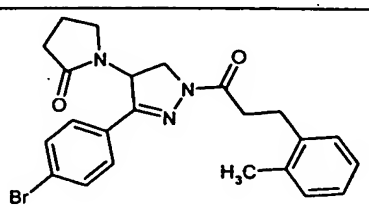
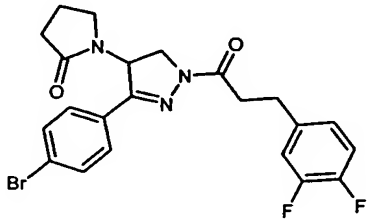
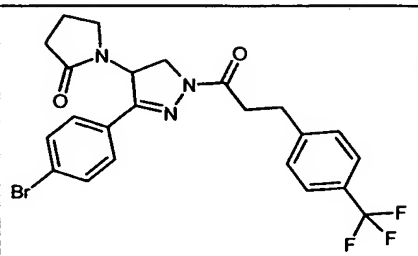
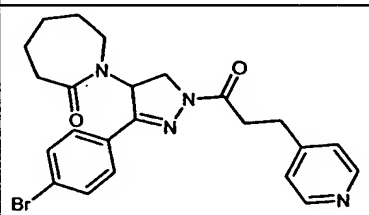
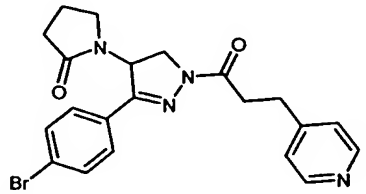
The compounds of Examples 27 to 60 are prepared analogously to Example 2.

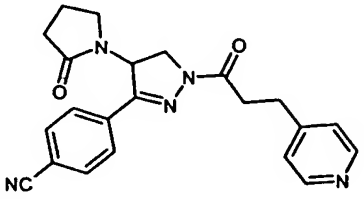
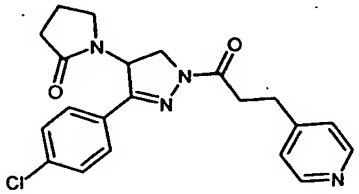
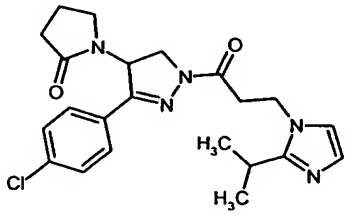
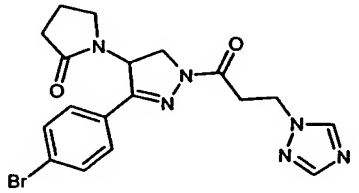
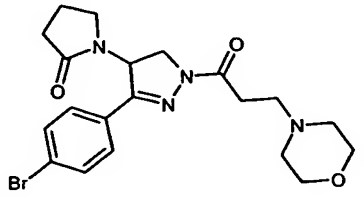
Ex-ample	Structure	Yield (reaction time)	R_t [min] (method)	Mass
27		64% (18h)	4.74 (1)	426 ESIpos $[M+H]^+$
28		62% (18h)	5.10 (1)	527 DCI (NH_3) $[M+NH_4]^+$
29		45% (18h)	5.28 (1)	561 DCI (NH_3) $[M+NH_4]^+$
30		42% (18h)	5.16 (1)	474 ESIpos $[M+H]^+$
31		54% (18h)	4.55 (1)	461 DCI (NH_3) $[M+H]^+$

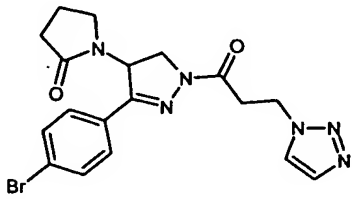
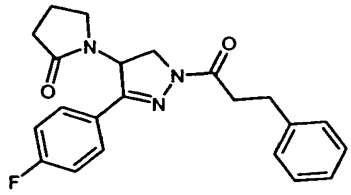
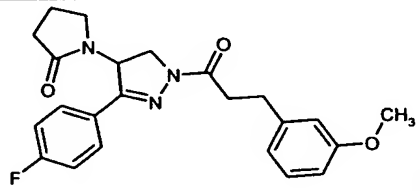
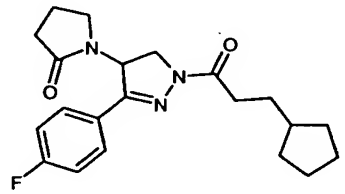
Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
32		44% (18h)	5.14 (1)	511 DCI (NH_3) $[M+NH_4]^+$
33		55% (18h)	4.68 (1)	501 DCI (NH_3) $[M+NH_4]^+$
34		51% (18h)	5.20 (1)	527 DCI (NH_3) $[M+NH_4]^+$
35		22% (18h)	5.37 (1)	511 DCI (NH_3) $[M+NH_4]^+$
36		26% (18h)	3.17 (2)	418 ESIpos $[M+H]^+$

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
37		38% (18h)	1.97 (2)	472 ESIpos $[M+H]^+$
38		49% (18h)	3.15 (2)	486 ESIpos $[M+H]^+$
39		50% (18h)	3.19 (2)	456 ESIpos $[M+H]^+$
40		35% (18h)	3.28 (3)	516 ESIpos $[M+H]^+$
41		19% (18h)	3.34 (3)	472 ESIpos $[M+H]^+$

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
42		30% (18h)	3.32 (3)	472 ESIpos $[M+H]^+$
43		34% (18h)	3.54 (3)	456 ESIpos $[M+H]^+$
44		28% (18h)	3.46 (3)	478 ESIpos $[M+H]^+$
45		30% (18h)	3.28 (3)	486 ESIpos $[M+H]^+$
46		26% (18h)	3.43 (3)	472 ESIpos $[M+H]^+$

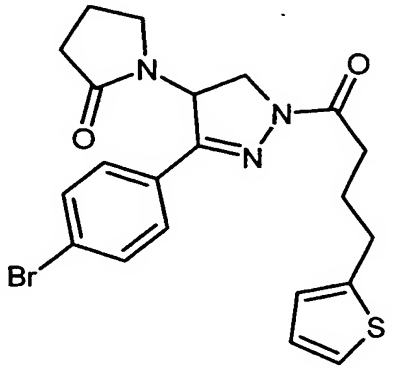
Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
47		20% (18h)	3.52 (3)	456 ESIpos $[M+H]^+$
48		9% (18h)	3.44 (3)	478 ESIpos $[M+H]^+$
49		29% (18h)	3.58 (3)	510 ESIpos $[M+H]^+$
50		28% (18h)	4.08 (6)	469 ESIpos $[M]^+$
51		52% (18h)	2.13 (3)	440 ESIpos $[M+H]^+$

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
52		31% (18h)	1.72 (3)	388 ESIpos $[M+H]^+$
53		27% (18h)	1.94 (3)	397 ESIpos $[M+H]^+$
54		62% (18h)	3.91 (1)	428 ESIpos $[M+H]^+$
55		47% (18h)	2.45 (5)	431 DCI (NH_3) $[M+H]^+$
56		25% (18h)	1.92 (5)	450 ESIpos $[M+H]^+$

Example	Structure	Yield (reaction time)	R_t [min] (method)	Mass
57		69% (18h)	2.47 (5)	431 DCI (NH_3) $[M+H]^+$
58		25% (18h)	4.61 (1)	380 ESIpos $[M+H]^+$
59		71% (18h)	4.56 (1)	410 ESIpos $[M+H]^+$
60		24% (18h)	4.95 (1)	372 ESIpos $[M+H]^+$

Example 61

1-{3-(4-Bromophenyl)-1-[4-(2-thienyl)butanoyl]-4,5-dihydro-1*H*-pyrazol-4-yl}pyrrolidin-2-one

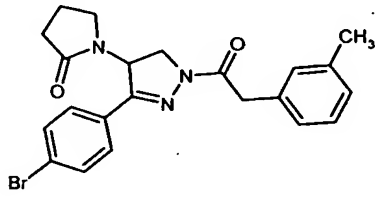


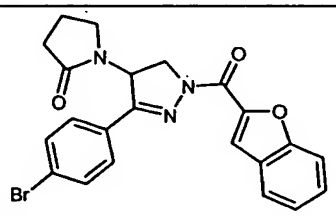
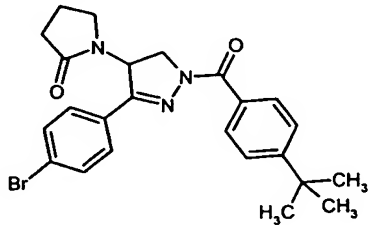
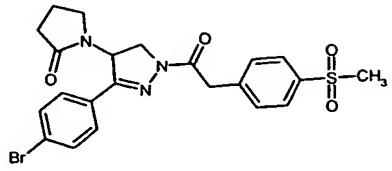
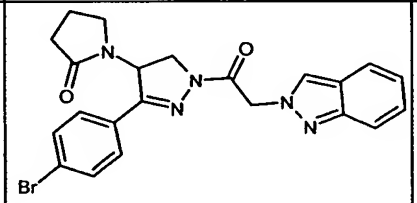
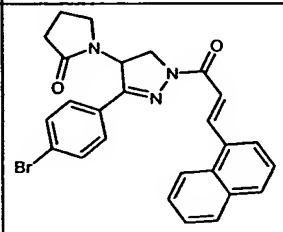
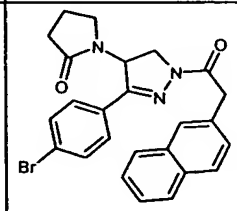
As a suspension in DMF, 13.5 mg (0.10 mmol) of HOBt, 28.8 mg (0.15 mmol) of EDC, 40.4 mg (0.40 mmol) of 4-methylmorpholine and 17.0 mg (0.10 mmol) of 4-thiophenebutanoic acid are added to 30.8 mg (0.10 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XII). The mixture is kept at RT for 18 h. Preparation HPLC (Grom-Sil RP18; mobile phase acetonitrile-water/0.1% formic acid gradient 30:70 -> 90:10) gives 18.9 mg (41% of theory) of product.

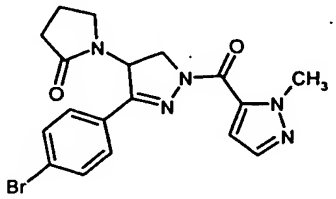
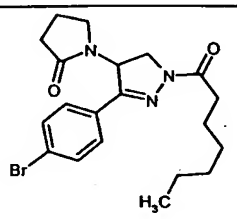
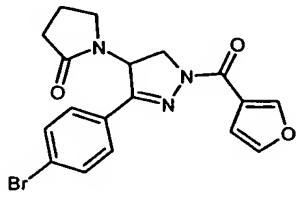
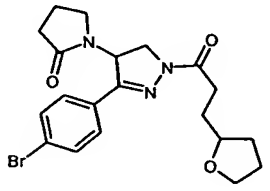
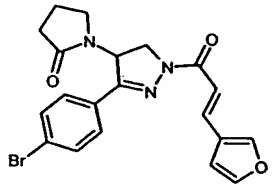
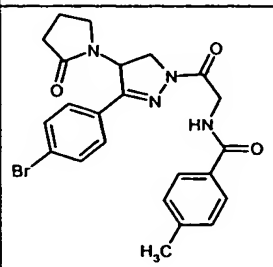
LC-MS (method 4): R_t = 2.19 min

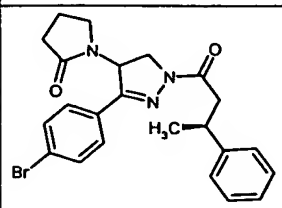
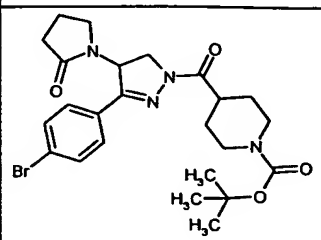
LC-MS (ESIpos): m/z = 460 $(M+H)^+$

The compounds of Examples 62 to 76 are prepared analogously to Example 61.

Example	**Structure**	**Yield**	**R_t [min] (method)**	**Mass ESIpos**
62		59%	2.16 (4)	440 $[M+H]^+$

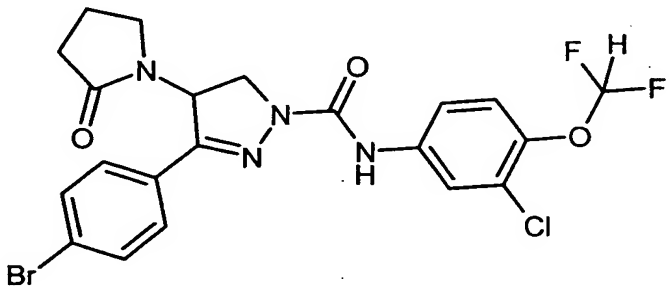
Example	Structure	Yield	R_t [min] (method)	Mass ESIpos
63		8%	2.13 (4)	452 $[M+H]^+$
64		44%	2.34 (4)	468 $[M+H]^+$
65		65%	1.85 (4)	505 $[M+H]^+$
66		44%	1.95 (4)	466 $[M+H]^+$
67		42%	2.37 (4)	488 $[M+H]^+$
68		38%	2.23 (4)	476 $[M+H]^+$

Example	Structure	Yield	R_t [min] (method)	Mass ESIpos
69		34%	1.82 (4)	416 $[M+H]^+$
70		58%	2.36 (4)	420 $[M+H]^+$
71		57%	1.95 (4)	402 $[M+H]^+$
72		60%	1.92 (4)	434 $[M+H]^+$
73		56%	2.05 (4)	428 $[M+H]^+$
74		74%	1.91 (4)	483 $[M+H]^+$

Example	Structure	Yield	R_t [min] (method)	Mass ESIpos
75		31%	2.21 (4)	454 $[M+H]^+$
76		30%	2.16 (4)	519 $[M+H]^+$

Example 77

N-(3-Chloro-4-difluoromethoxyphenyl)-3-(4-bromophenyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-carboxamide



3060 mg (13.95 mmol) of 2-chloro-1-difluoromethoxyphenyl 4-isocyanate are added to a solution of 4300 mg (13.95 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XII) in 140 ml of dichloromethane. The mixture is stirred at RT for 1 h. After concentration, the mixture is stirred with diethyl ether and filtered, and the residue that remains is washed with diethyl ether. The resulting solid is purified by silica gel chromatography (mobile phase dichloromethane/methanol gradient 95:5). The residue is then triturated with diethyl ether and filtered off and washed with diethyl ether. This gives 6500 mg (88% of theory) of product.

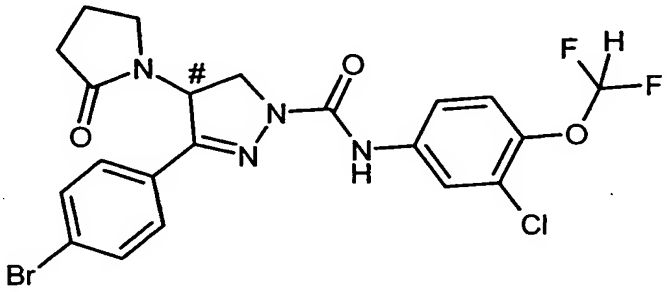
HPLC (method 1): R_t = 4.94 min

MS (ESIpos): m/z = 527 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.68-1.98 (m, 2H), 2.12-2.34 (m, 2H), 2.48-2.54 (m, 1H), 2.72-2.80 (m, 1H), 3.95-4.10 (m, 2H), 5.98 (dd, 1H), 7.19 (dd, 1H), 7.33 (d, 1H), 7.68-7.82 (m, 5H), 7.99 (s, 1H) , 9.42 (s, 1H) ppm.

Example 78

N-(3-chloro-4-difluoromethoxyphenyl)-3-(4-bromophenyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-carboxamide

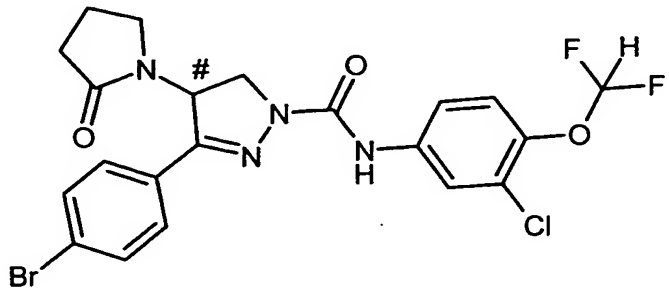


Separation of the enantiomers of Example 77 according to method 8 gives the title compound as enantiomer A (97.9% ee).

HPLC (method 9): R_t = 5.35 min.

Example 79

N-(3-chloro-4-difluoromethoxyphenyl)-3-(4-bromophenyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-carboxamide

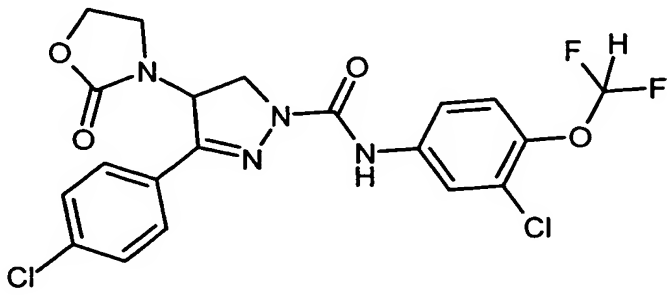


Separation of the enantiomers of Example 77 according to method 8 gives the title compound as enantiomer B (97.9% ee).

HPLC (method 9): R_t = 7.56 min.

Example 80

N-[3-Chloro-4-(difluoromethoxy)phenyl]-3-(4-chlorophenyl)-4-(2-oxo-1,3-oxazolidin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide



A solution of 45 mg (0.17 mmol) of 3-[3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]-1,3-oxazolidin-2-one in 2 ml of dichloromethane is added to 45 mg (0.20 mmol) of 2-chloro-1-difluoromethoxyphenyl 4-isocyanate. The mixture is stirred at RT for 18 h. After concentration, the mixture is stirred with DMSO and methanol and filtered, and the residue that remains is washed twice with diethyl ether. This gives 48 mg (58% of theory) of product.

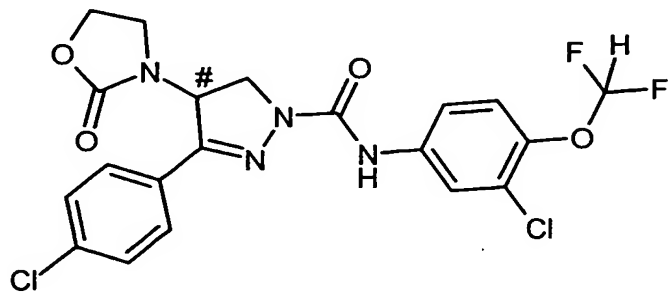
HPLC (method 1): R_t = 4.97 min

MS (ESIpos): m/z = 485 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.13 (ddd, 1H), 3.52 (ddd, 1H), 4.08-4.38 (m, 4H), 5.88 (dd, 1H), 6.48 (dd, 1H), 7.17-7.49 (m, 4H), 7.72-7.83 (m, 3H), 8.01 (s, 1H) ppm.

Example 81

N-[3-Chloro-4-(difluoromethoxy)phenyl]-3-(4-chlorophenyl)-4-(2-oxo-1,3-oxazolidin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide

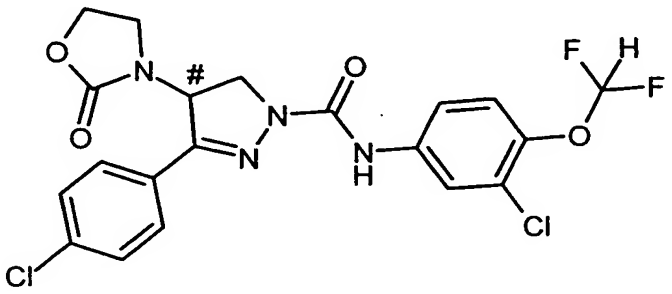


Separation of the enantiomers of Example 80 according to method 10 gives the title compound as enantiomer A (>99% ee).

HPLC (method 11): R_t = 2.74 min.

Example 82

N-[3-Chloro-4-(difluoromethoxy)phenyl]-3-(4-chlorophenyl)-4-(2-oxo-1,3-oxazolidin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide

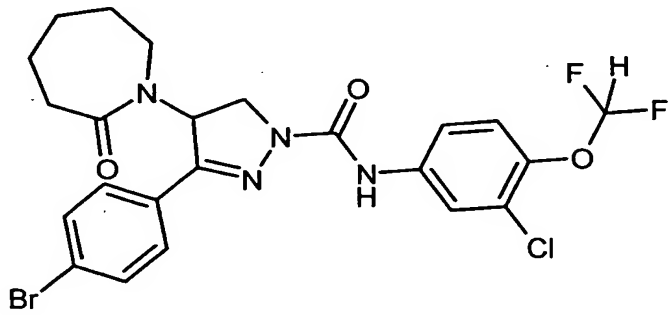


Separation of the enantiomers of Example 80 according to method 10 gives the title compound as enantiomer B (96.8% ee).

HPLC (method 11): R_t = 4.09 min.

Example 83

N-(3-Chloro-4-difluoromethoxyphenyl)-3-(4-bromophenyl)-4-(2-oxoazepan-1-yl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide



A solution of 79.4 mg (0.24 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-4-yl]azepan-2-one (Example XXI) in 2.0 ml of dichloromethane is added to 62.2 mg (0.28 mmol) of 2-chloro-1-difluoromethoxyphenyl-4-isocyanate. The mixture is stirred at RT for 18 h. After concentration,

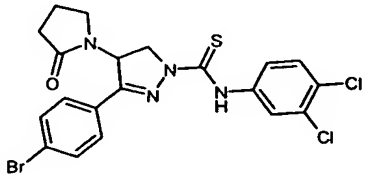
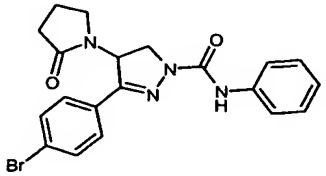
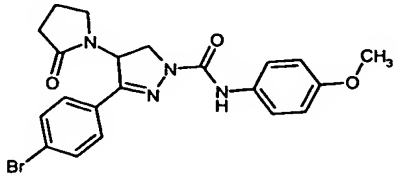
the residue is stirred with 1 ml of warm DMSO and 0.4 ml of warm methanol and filtered off with suction through a silica gel cartridge, and the residue that remains is washed with diethyl ether. This gives 119.5 mg (91% of theory) of product.

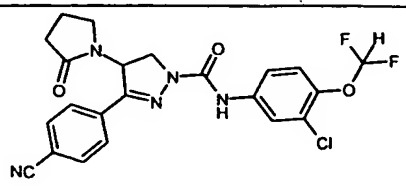
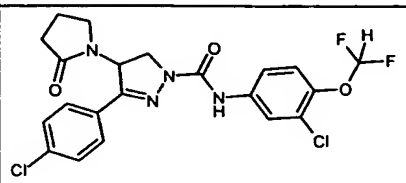
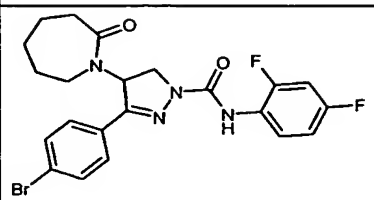
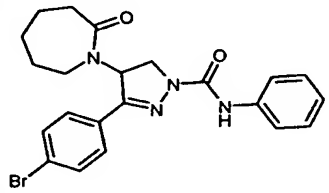
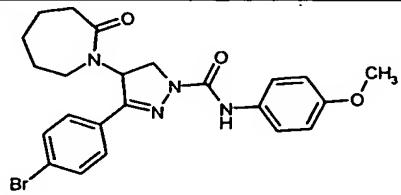
HPLC (method 1): R_t = 5.21 min

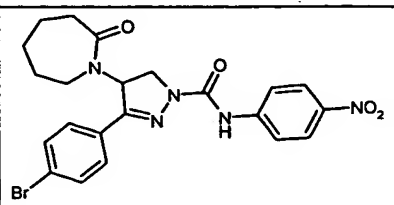
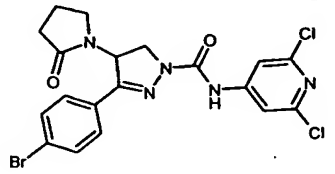
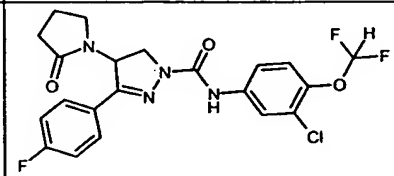
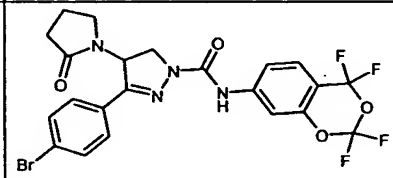
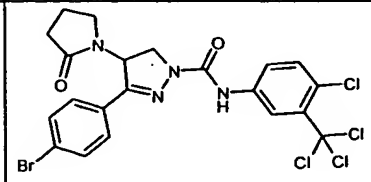
MS [DCI (NH_3)]: m/z = 572 $(M+NH_4)^+$

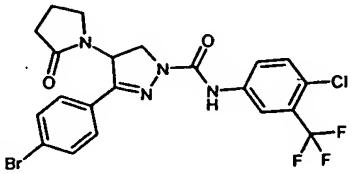
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.98-1.21 (m, 1H), 1.34-1.81 (m, 5H), 2.55 (dd, 2H), 3.11 (dddd, 2H), 4.07 (dddd, 2H), 6.49 (dd, 1H), 6.63 (dd, 1H), 7.21 (dd, 1H), 7.44 (dd, 1H), 7.62 (m_c, 4H), 7.77 (dd, 1H), 8.01 (s, 1H) ppm.

The compounds of Examples 84 to 97 are prepared analogously to Example 83.

Example	**Structure**	**Yield** **reaction time**	**R_t [min]** **(method)**	**Mass**
84		80% 18 h	5.38 (1)	511 DCI (NH_3) $[M+H]^+$
85		60% 18 h	4.75 (1)	444 DCI (NH_3) $[M+NH_4]^+$
86		52% 18 h	4.66 (1)	457 DCI (NH_3) $[M+H]^+$

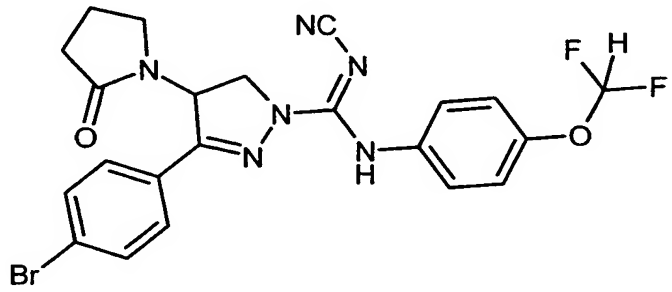
Example	Structure	Yield reaction time	R_t [min] (method)	Mass
87		87% 18 h	4.66 (1)	472 ESIpos $[M+H]^-$
88		79% 18 h	4.93 (1)	483 ESIpos $[M+H]^+$
89		62% 18 h	5.15 (1)	491 ESIpos $[M+H]^+$
90		83% 18 h	5.01 (1)	455 ESIpos $[M+H]^+$
91		67% 18 h	4.93 (1)	485 ESIpos $[M+H]^+$

Example	Structure	Yield reaction time	R_t [min] (method)	Mass
92		61% 18 h	4.92 (1)	500 EI $[M]^+$
93		45% 18 h	3.46 (3)	498 ESIpos $[M+H]^+$
94		66% 18 h	4.79 (1)	467 ESIpos $[M+H]^+$
95		73% 24 h	5.19 (1)	574 DCI (NH_3) $[M+NH_4]^+$
96		80% 24 h	4.35 (6)	596 DCI (NH_3) $[M+NH_4]^+$

Example	Structure	Yield reaction time	R_t [min] (method)	Mass
97		85% 24 h	5.18 (6)	546 DCI (NH_3) $[M+NH_4]^+$

Example 98

3-(4-Bromophenyl)-*N*-cyano-*N'*-(4-difluoromethoxyphenyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-carboxamidine



A suspension of 150 mg (0.33 mmol) of 3-(4-bromophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-phenylimidate (Example XXII) and 105 mg (0.66 mmol) of 4-difluoromethoxyphenylamine in 2 ml of ethanol is heated under reflux for 3 d. After cooling, the resulting precipitate is filtered off with suction and washed with a little diethyl ether. The material is pre-purified by preparative HPLC (Grom-Sil RP18 column; mobile phase: water/0.3% formic acid-acetonitrile gradient: 90:10 -> 10:90). The product fractions are combined and subjected to fine purification by another preparative HPLC (Grom-Sil RP18 column; mobile phase: water-acetonitrile gradient: 90:10 -> 10:90). This gives 19 mg (11% of theory) of the desired product.

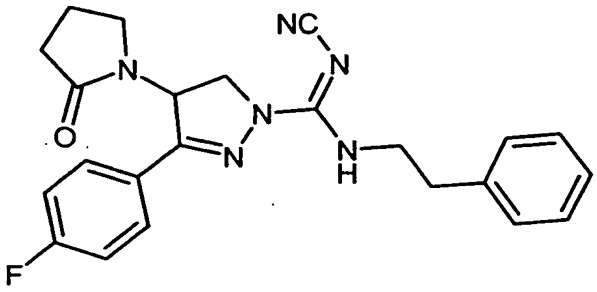
HPLC (method 1): R_t = 4.61 min

MS [DCI (NH_3)]: m/z = 517 $(M+H)^+$

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.83-2.20 (m, 2H), 2.24-2.57 (m, 2H), 2.94 (ddd, 1H), 3.40 (ddd, 1H), 4.33 (dd, 1H), 4.53 (dd, 1H), 6.25 (dd, 1H), 6.53 (t, 1H), 7.16 (d, 2H), 7.44 (d, 2H) 7.53-7.72 (m, 4H), 8.06 (s, 1H) ppm.

Example 99

N'-Cyano-3-(4-fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydropyrazole-1-carboxamidine



A suspension of 60 mg (0.15 mmol) of 3-(4-fluorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-phenylimidate (Example XXIII) and 37 mg (0.31 mmol) of (2-phenylethyl)amine in 2 ml of ethanol is heated under reflux for 3 d. After cooling, the solvent is removed and the resulting precipitate is stirred wih 2 ml of diethyl ether. This gives 61 mg (95% of theory) of the desired product.

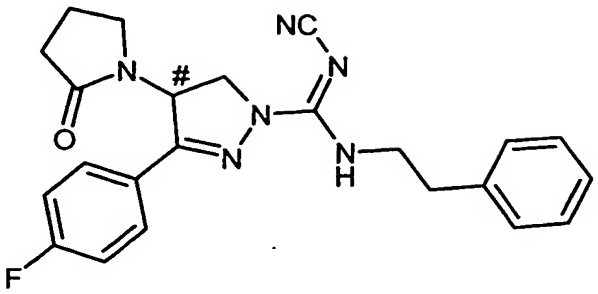
HPLC (method 1): R_t = 4.46 min

MS (ESIpos): m/z = 419 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.79-2.11 (m, 2H), 2.22-2.49 (m, 2H), 2.85 (ddd, 1H), 2.93-3.02 (m, 2H), 3.32 (ddd, 1H), 3.85 (q, 2H), 4.15 (dd, 1H), 4.40 (dd, 1H), 6.13 (dd, 1H), 6.39 (t, 1H), 7.06-7.15 (m, 2H), 7.25-7.39 (m, 5H) 7.63-7.70 (m, 2H) ppm.

Example 100

N'-Cyano-3-(4-fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydropyrazole-1-carboxamidine

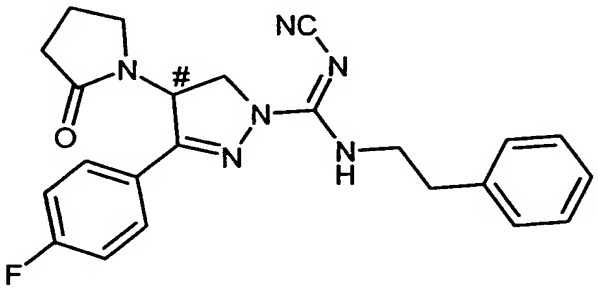


Separation of the enantiomers of Example 99 according to method 12 gives the title compound as enantiomer A (99.3% ee).

HPLC (method 12): R_t = 7.39 min.

Example 101

N'-Cyano-3-(4-fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydropyrazole-1-carboxamidine

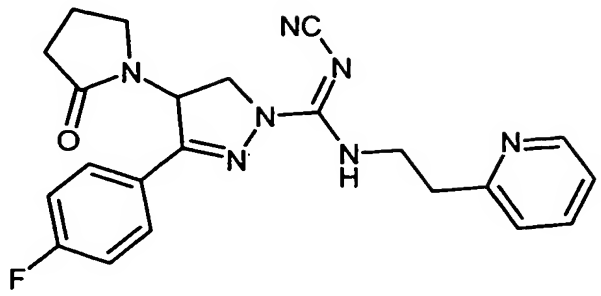


Separation of the enantiomers of Example 99 according to method 12 gives the title compound as enantiomer B (99.5% ee).

HPLC (method 12): R_t = 10.46 min.

Example 102

N'-Cyano-3-(4-fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-pyridin-2-ylethyl)-4,5-dihydropyrazole-1-carboxamidine



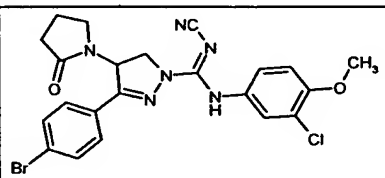
A suspension of 40 mg (0.10 mmol) of 3-(4-fluorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-phenylimidate (Example XXIII) and 25 mg (0.20 mmol) of (2-pyridin-2-ylethyl)amine in 1.5 ml of ethanol is heated under reflux for 1 d. After cooling, the solvent is removed and the resulting precipitate is taken up in 1 ml of diethyl ether and 0.5 ml of ethanol. Silica gel chromatography (mobile phase dichloromethane/ethanol 40:1) gives 13 mg (31% of theory) of the desired product.

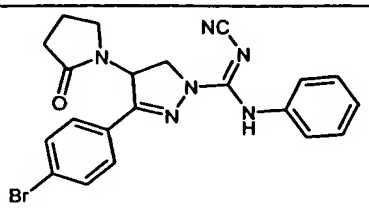
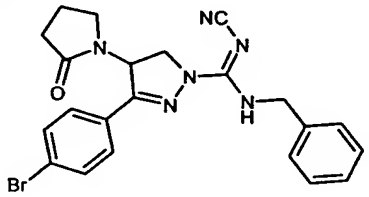
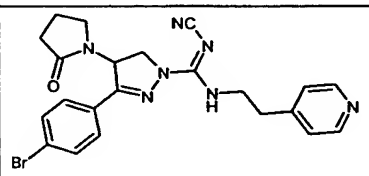
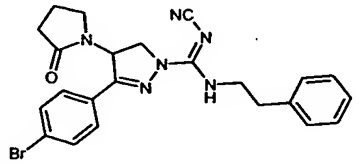
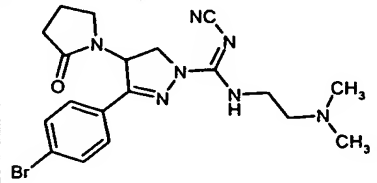
HPLC (method 1): $R_t = 3.62$ min

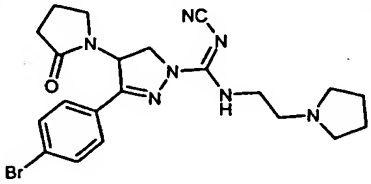
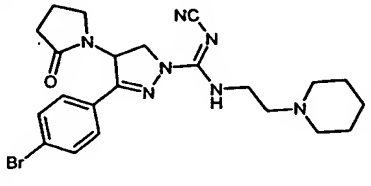
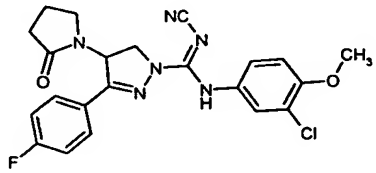
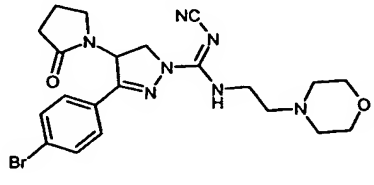
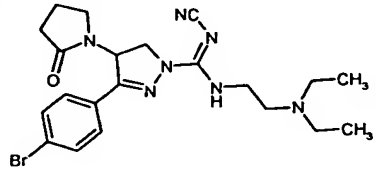
MS (ESIpos): m/z = 420 $(M+H)^+$

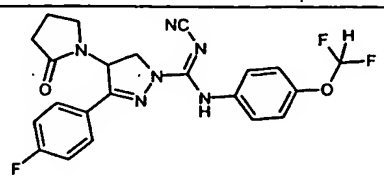
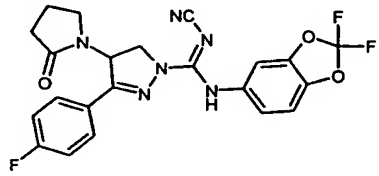
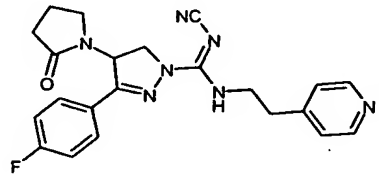
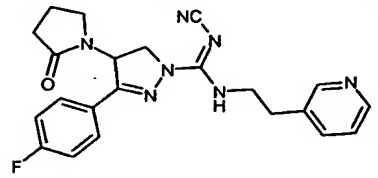
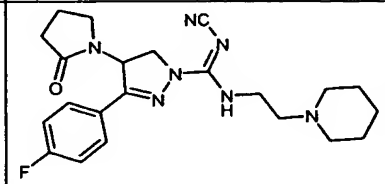
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.79-2.11 (m, 2H), 2.22-2.49 (m, 2H), 2.85 (ddd, 1H), 2.93-3.00 (m, 2H), 3.31 (ddd, 1H), 3.85 (q, 2H), 4.15 (dd, 1H), 4.40 (dd, 1H), 6.13 (dd, 1H), 6.39 (t, 1H), 7.06-7.15 (m, 2H), 7.25-7.39 (m, 4H) 7.63-7.70 (m, 2H) ppm.

The compounds of Examples 103 to 118 are prepared analogously to Example 98.

Example	**Structure**	**Yield** **reaction time**	**R_t [min]** **(method)**	**Mass**
103		67% 3 d	4.58 (1)	515 DCI (NH_4) $[M+H]^+$

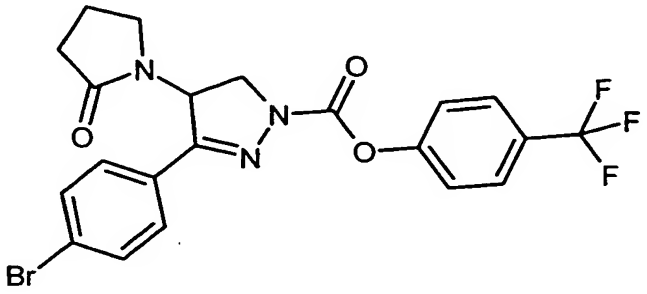
Example	Structure	Yield reaction time	R_t [min] (method)	Mass
104		63% 3 d	4.43 (1)	451 DCI (NH_4) $[M+H]^+$
105		83% 3 d	4.56 (1)	465 ESIpos $[M+H]^+$
106		66% 3 d	4.56 (1)	480 ESIpos $[M+H]^+$
107		60% 3 d	4.71 (1)	479 ESIpos $[M+H]^+$
108		38% 1 d	3.72 (1)	446 ESIpos $[M+H]^+$

Example	Structure	Yield reaction time	R_t [min] (method)	Mass
109		85% 1 d	3.81 (1)	472 ESIpos $[M+H]^+$
110		75% 1 d	3.87 (1)	486 ESIpos $[M+H]^+$
111		59% 3 d	4.36 (1)	455 ESIpos $[M+H]^+$
112		73% 1 d	3.74 (1)	488 DCI (NH_4) $[M+H]^+$
113		54% 1 d	3.84 (1)	476 DCI (NH_4) $[M+H]^+$

Example	Structure	Yield reaction time	R_t [min] (method)	Mass
114		20% 3 d	4.38 (1)	457 DCI (NH_4) $[M+H]^+$
115		11% 3 d	4.54 (1)	471 ESIpos $[M+H]^+$
116		70% 1 d	3.59 (1)	420 ESIpos $[M+H]^+$
117		31% 1 d	3.65 (1)	420 ESIpos $[M+H]^+$
118		32% 3 d	3.71 (1)	426 ESIpos $[M+H]^+$

Example 119

4-Trifluoromethylphenyl 3-(4-bromophenyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-carboxylate



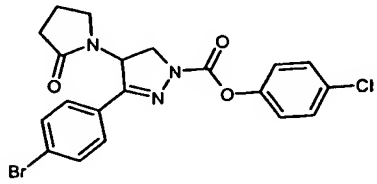
At RT, 0.04 ml (0.30 mmol) of TEA and 67.4 mg (0.30 mmol) of 4-trifluoromethylphenyl chloroformate are added to a solution of 77 mg (0.25 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XII) in dichloromethane. After 2 h, the solvent is removed under reduced pressure and the crude product is purified by preparative HPLC (Grom-Sil RP18 column; mobile phase: water/0.3% formic acid-acetonitrile gradient: 70:30 -> 10:90). This gives 65.6 mg (53% of theory) of the desired product.

HPLC (method 1): R_t = 4.94 min

MS [DCI (NH_3)]: m/z = 513 $(M+NH_4)^+$

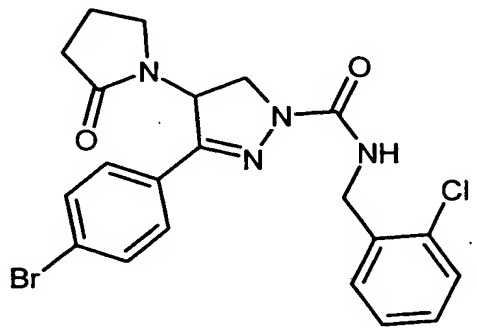
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.83-2.12 (m, 2H), 2.27-2.51 (m, 2H), 2.98 (ddd, 1H), 3.35 (ddd, 1H), 3.98-4.10 (m, 1H), 4.15-4.29 (m, 1H), 6.15 (dd, 1H), 7.37 (d, 2H), 7.51-7.59 (m, 2H), 7.64-7.74 (m, 4H) ppm.

Example 120 is prepared analogously to Example 119.

Example	**Structure**	**Yield**	**R_t [min] (method)**	**Mass DCI (NH_3)**
120		76%	4.82 (1)	479 $[M+NH_4]^+$

Example 121

N-(2-Chlorobenzyl)-3-(4-bromophenyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydropyrazole-1-carboxamide



A mixture of 50 mg (0.16 mmol) of 1-[3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XII) and 32.3 mg (0.19 mmol) of 2-chlorobenzyl isocyanate in 2 ml of dichloromethane is stirred at RT for 18 h. After concentration, preparative HPLC (Grom-Sil RP18; mobile phase acetonitrile-water/0.3% formic acid gradient 10:90 -> 90:10) 29.1 mg (37% of theory) of the product.

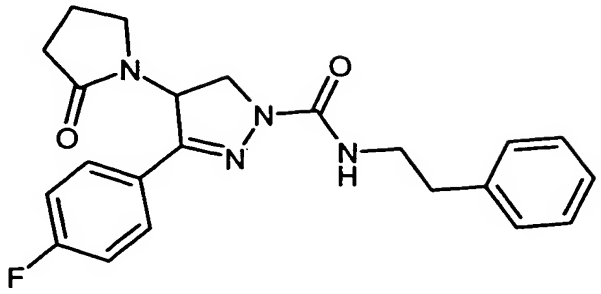
HPLC (method 1): $R_t = 4.85$ min

MS (ESIpos): m/z = 475 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.80-2.05 (m, 2H), 2.36 (m_c, 2H), 2.89 (dt, 1H), 3.29 (dt, 1H), 3.98 (dd, 1H), 4.04 (dd, 1H), 4.62 (d, 2H), 6.04 (dd, 1H), 6.52 (t, 1H), 7.22-7.29 (m, 2H), 7.36-7.48 (m, 2H), 7.52 (d, 2H), 7.59 (d, 2H) ppm.

Example 122

3-(4-Fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydro-1H-pyrazole-1-carboxamide



A solution of 60 mg (0.24 mmol) of 1-[3-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XIII) in 2 ml of dichloromethane is added to 43 mg (0.29 mmol) of (2-isocyanatoethyl)benzene, and the mixture is stirred at RT for 18 h. After concentration, preparative HPLC (Grom-Sil RP18; mobile phase acetonitrile water/0.3% formic acid gradient 10:90 -> 90:10) gives 42 mg (44% of theory) of the product.

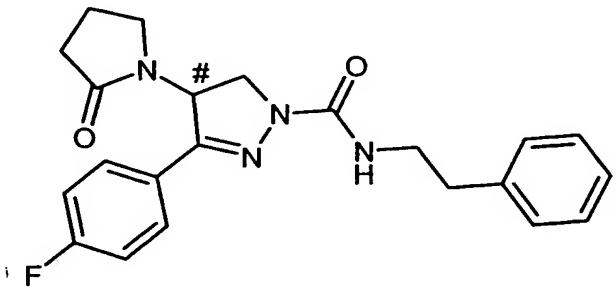
HPLC (method 1): R_t = 4.48 min

MS (ESIpos): m/z = 395 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.78-2.08 (m, 2H), 2.34 (m_c, 2H), 2.83-2.95 (m, 3H), 3.28 (ddd, 1H), 3.60 (m_c, 2H), 3.91-4.06 (m, 2H), 6.02 (dd, 1H), 6.09 (t, 1H), 7.04-7.12 (m, 2H), 7.21-7.28 (m, 3H), 7.30-7.35 (m, 2H), 7.63-7.72 (m, 2H) ppm.

Example 123

3-(4-Fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

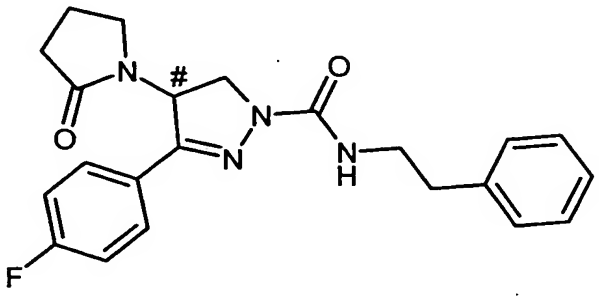


Separation of the enantiomers of Example 122 according to method 12 gives the title compound as enantiomer A (99.6% ee).

HPLC (method 12): R_t = 6.51 min.

Example 124

3-(4-Fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydro-1H-pyrazole-1-carboxamide

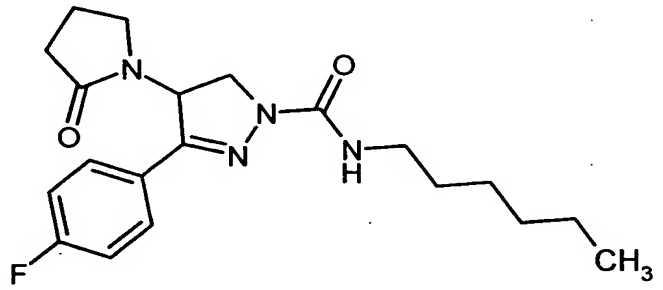


Separation of the enantiomers of Example 122 according to method 12 gives the title compound as enantiomer B (99.5% ee).

HPLC (method 12): R_t = 12.30 min.

Example 125

3-(4-Fluorophenyl)-*N*-hexyl-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide



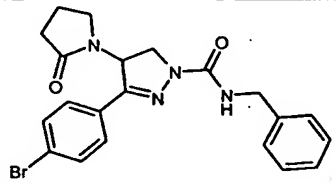
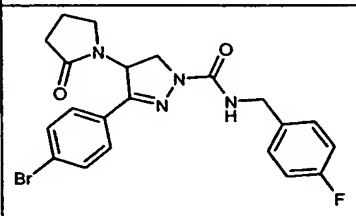
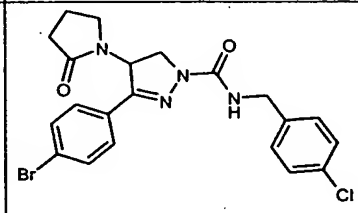
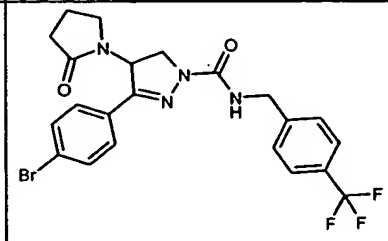
A solution of 50 mg (0.20 mmol) of 1-[3-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-4-yl]pyrrolidin-2-one (Example XIII) in 2 ml of dichloromethane is added to 31 mg (0.24 mmol) of hexyl isocyanate, and the mixture is stirred at RT for 18 h. After concentration, preparative HPLC (Grom-Sil RP18; mobile phase acetonitrile-water/0.3% formic acid gradient 10:90 -> 90:10) gives 31 mg (39% of theory) of the product.

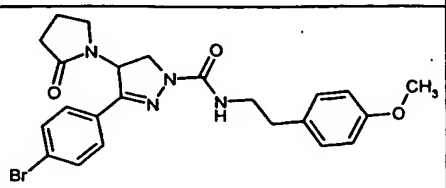
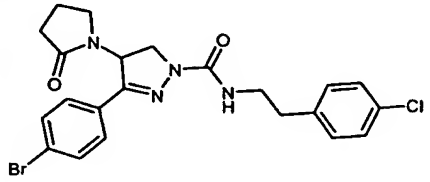
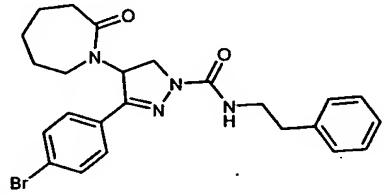
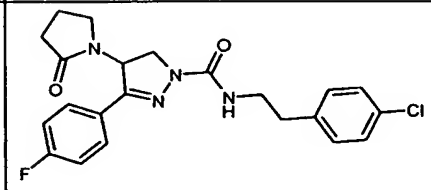
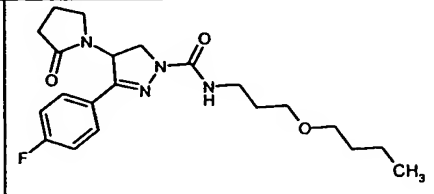
HPLC (method 3): R_t = 2.55 min

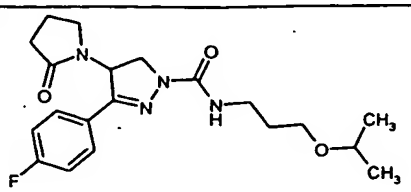
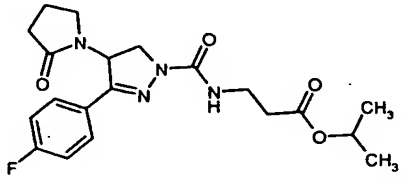
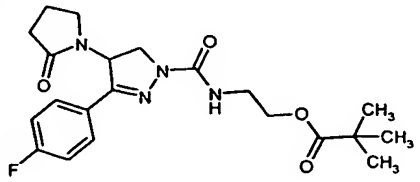
MS (ESIpos): m/z = 375 $(M+H)^+$

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, 3H), 1.20-1.46 (m, 6H), 1.51-1.68 (m, 2H), 1.73-2.08 (m, 2H), 2.37 (m_c, 2H), 2.90 (ddd, 1H), 3.22-3.39 (m, 3H), 3.91-4.06 (m, 2H), 5.93-6.09 (m, 2H), 7.02-7.15 (m, 2H), 7.66-7.78 (m, 2H) ppm.

The compounds of Examples 126 to 137 are prepared analogously to Example 122.

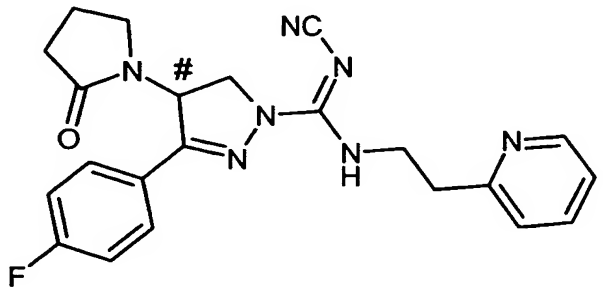
Example	**Structure**	**Yield**	**R_t [min] (method)**	**Mass**
126		55%	4.63 (1)	458 DCI(NH_3) $[M+NH_4]^+$
127		35%	4.68 (1)	459 ESIpos $[M+H]^+$
128		30%	4.85 (1)	492 DCI(NH_3) $[M+NH_4]^+$
129		24%	4.79 (1)	509 ESIpos $[M+H]^+$

Example	Structure	Yield	R_t [min] (method)	Mass
130		50%	3.20 (3)	487 ESIpos $[M+H]^+$
131		54%	3.47 (3)	485 ESIpos $[M+H]^+$
132		44%	3.41 (3)	491 ESIpos $[M+H]^+$
133		61%	4.67 (1)	429 ESIpos $[M+H]^+$
134		32%	3.41 (3)	491 ESIpos $[M+H]^+$

Example	Structure	Yield	R_t [min] (method)	Mass
135		40%	2.14 (3)	391 ESIpos $[M+H]^+$
136		39%	2.10 (3)	405 ESIpos $[M+H]^+$
137		37%	2.23 (3)	419 ESIpos $[M+H]^+$

Example 138

N'-Cyano-3-(4-fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-pyridin-2-ylethyl)-4,5-dihydropyrazole-1-carboxamidine

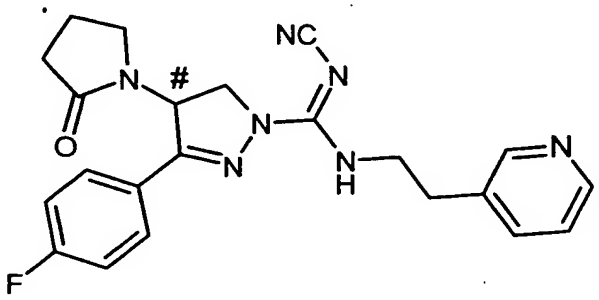


Separation of the enantiomers of Example 102 according to method 19 gives the title compound as enantiomer 2 (99.3% ee).

HPLC (method 19): R_t = 21.97 min. (second fraction)

Example 139

N'-Cyano-3-(4-fluorophenyl)-4-(2-oxopyrrolidin-1-yl)-*N*-(2-pyridin-3-ylethyl)-4,5-dihydropyrazole-1-carboxamidine

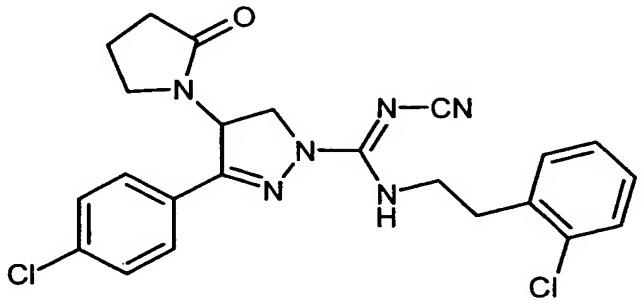


Separation of the enantiomers of Example 117 according to method 20 gives the title compound as enantiomer 2 (100% ee).

HPLC (method 20): R_t = 21.23 min. (second fraction)

Example 140

3-(4-Chlorophenyl)-*N*-[2-(2-chlorophenyl)ethyl]-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.076 g (0.49 mmol) of 2-(2-chlorophenyl)ethylamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a

solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.082 g (71% of theory) of the product.

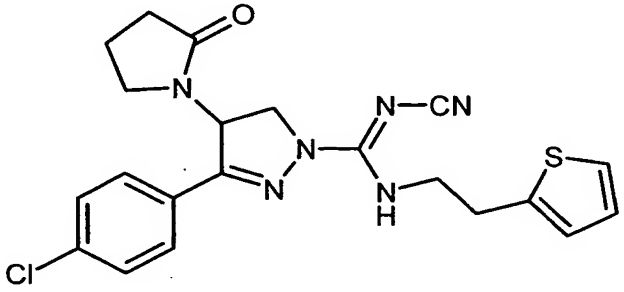
LC-MS (method 13): R_t = 2.6 min.

MS (ESI pos): m/z = 469 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.81 (m, 1H), 1.89 (m, 1H), 2.21 (m, 2H), 2.75 (m, 1H), 3.02 (t, 2H), 3.25 (m, 1H), 3.64 (m, 2H), 4.24 (m, 2H), 6.03 (dd, 1H), 7.29 (m, 2H), 7.41 (m, 2H), 7.59 (d, 2H), 7.80 (d, 2H), 8.09 (t, 1H).

Example 141

3-(4-Chlorophenyl)-*N*'-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-[2-(2-thienyl)ethyl]-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.062 g (0.49 mmol) of 2-(2-thienyl)ethanamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.081 g (75% of theory) of the product.

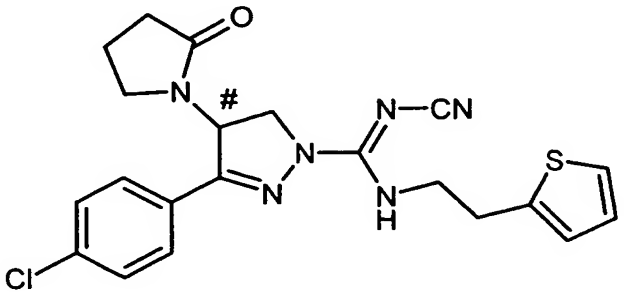
LC-MS (method 13): R_t = 2.43 min.

MS (ESI pos): m/z = 441 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.78 (m, 1H), 1.92 (m, 1H), 2.19 (m, 2H), 2.76 (m, 1H), 3.10 (t, 2H), 3.28 (m, 1H), 3.61 (m, 2H), 4.20 (m, 2H), 6.04 (dd, 1H), 6.95 (m, 2H), 7.35 (dd, 1H), 7.59 (d, 2H), 7.76 (d, 2H), 8.10 (t, 1H).

Example 142

3-(4-Chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-[2-(2-thienyl)ethyl]-4,5-dihydro-1H-pyrazole-1-carboximidamide

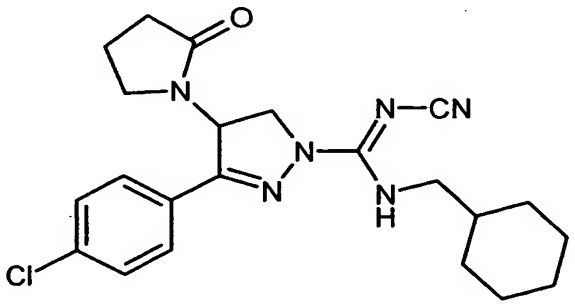


Separation of the enantiomers of Example 141 acccording to method 18 gives the title compound as enantiomer 2 (99.2% ee).

HPLC (method 18): R_t = 10.83 min. (second fraction)

Example 143

3-(4-Chlorophenyl)-*N'*-cyano-*N*-(cyclohexylmethyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.055 g (0.49 mmol) of 1-cyclohexylmethanamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.057 g (60% of theory) of the product.

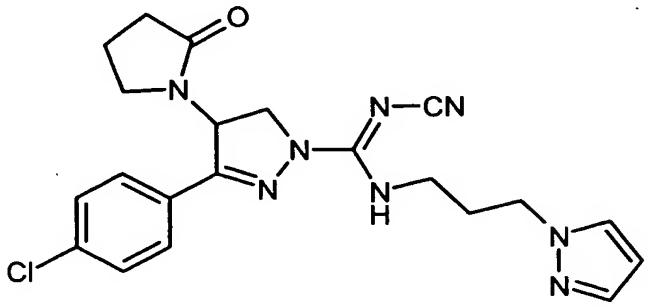
LC-MS (method 13): R_t = 2.68 min.

MS (ESI pos): m/z = 427 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.93 (m, 2H), 1.17 (m, 3H), 1.68 (m, 7H), 1.91 (m, 1H), 2.22 (m, 2H), 2.76 (m, 1H), 3.27 (m, 3H), 4.20 (m, 2H), 6.01 (dd, 1H), 7.57 (d, 2H), 7.77 (d, 2H), 7.95 (t, 1H).

Example 144

3-(4-Chlorophenyl)-*N*'-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-[3- (1H-pyrazol-1-yl)propyl]-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.062 g (0.49 mmol) of 3-(1H-pyrazol-1-yl)propan-1-amine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.071 g (66% of theory) of the product.

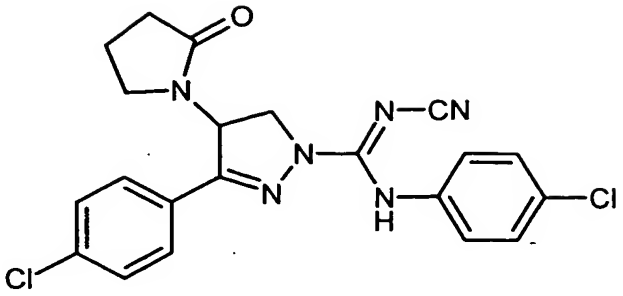
LC-MS (method 13): R_t = 2.01 min.

MS (ESI pos): m/z = 439 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.95 (m, 1H), 1.88 (m, 1H), 2.06 (m, 2H), 2.21 (m, 2H), 2.77 (m, 1H), 3.3 (m, 3H), 4.22 (m, 4H), 6.03 (m, 1H), 6.23 (t, 1H), 7.44 (d, 1H), 7.58 (d, 2H), 7.75 (d, 1H), 7.80 (d, 2H), 7.99 (t, 1H).

Example 145

N,3-Bis(4-chlorophenyl)-*N*'-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.062 g (0.49 mmol) of 4-chloroaniline are dissolved in 3 ml of ethanol and heated at reflux for six days. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.039 g (36% of theory) of the product.

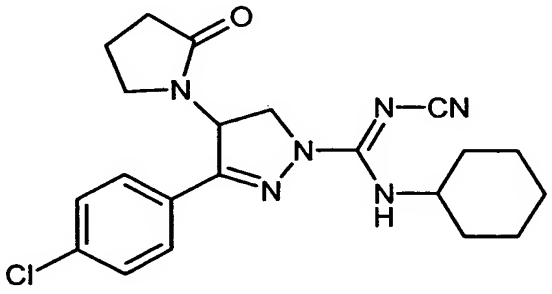
LC-MS (method 14): R_t = 2.27 min.

MS (ESI pos): m/z = 441 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.80 (m, 1H), 1.90 (m, 1H), 2.22 (m, 2H), 2.81 (m, 1H), 3.39 (m, 1H), 4.29 (m, 2H), 6.08 (dd, 1H), 7.42 (dd, 4 H), 7.59 (d, 2H), 7.79 (d, 2H), 9.82 (s, 1H).

Example 146

3-(4-Chlorophenyl)-*N'*-cyano-*N*-cyclohexyl-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.048 g (0.49 mmol) of cyclohexylamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product

is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.080 g (79% of theory) of the product.

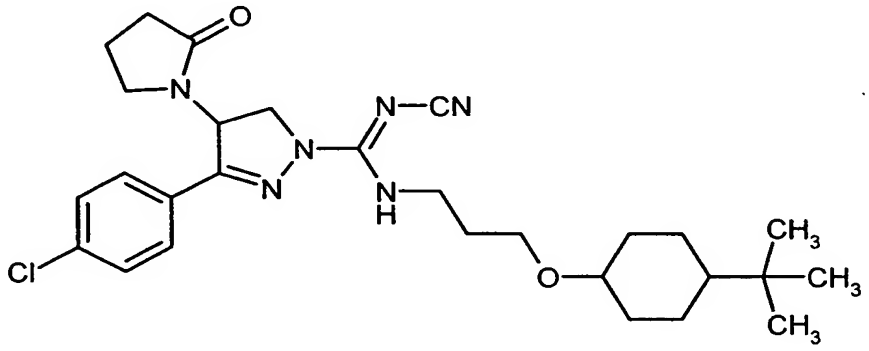
LC-MS (method 13): R_t = 2.49 min.

MS (ESI pos): m/z = 413 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.12 (m, 1H), 1.29 (m, 2H), 1.41 (m, 2H), 1.15 (d, 1H), 1.74 (m, 3H), 1.87 (m, 3H), 2.23 (m, 2H), 2.76 (m, 1H), 3.31 (m, 1H), 3.88 (m, 1H), 4.20 (m, 2H), 6.02 (dd, 1H), 7.53 (d, 1H), 7.56 (d, 2H), 7.79 (d, 2H).

Example 147

N-{3-[(4-*tert*-Butylcyclohexyl)oxy]propyl}-3-(4-chlorophenyl)-*N*'-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.261 g (1.22 mmol) of 3-[(4-*tert*-butylcyclohexyl)oxy]propan-1-amine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the solvent is removed under reduced pressure and the product is purified by preparative HPLC. This gives 0.12 g (93% of theory) of the product.

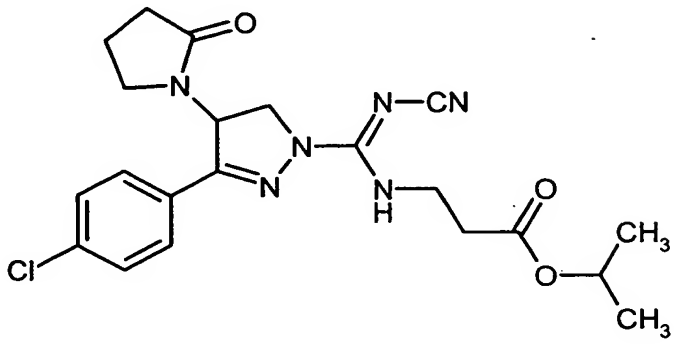
LC-MS (method 13): R_t = 3.16 min.

MS (ESI pos): m/z = 527 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.80 (s, 9H), 1.00 (m, 4H), 1.75 (m, 6H), 1.88 (m, 2H), 1.98 (m, 2H), 2.22 (m, 2H), 2.76 (m, 1H), 3.10 (m, 1H), 3.47 (m, 4H), 4.20 (m, 2H), 6.02 (dd, 1H), 7.56 (d, 2H), 7.87 (d, 2H), 7.87 (t, 1H).

Example 148

Isopropyl *N*-[(E)-[3-(4-chlorophenyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazol-1-yl](cyanoimino)methyl]beta-alaninate



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazol-1-carboximidoate und 0.064 g (0.49 mmol) of isopropyl beta-alaninate are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the solvent is removed under reduced pressure and the product is purified by preparative HPLC. This gives 0.1 g (92% of theory) of the product.

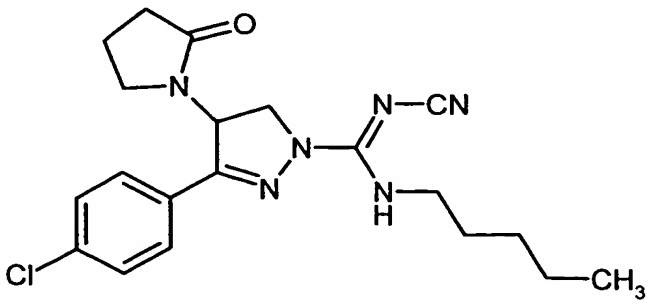
LC-MS (method 14): R_t = 2.08 min.

MS (ESI pos): m/z = 445 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.19 (d, 6H), 1.77 (m, 1H), 1.91 (m, 1H), 2.23 (m, 2H), 2.59 (t, 2H), 2.76 (m, 1H), 3.26 (m, 1H), 3.61 (m, 2H), 4.23 (m, 2H), 4.91 (m, 1H), 6.04 (dd, 1H), 7.58 (d, 2H), 7.75 (d, 2H), 7.92 (t, 1H).

Example 149

3-(4-Chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-pentyl-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.042 g (0.49 mmol) of *n*-pentylamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the solvent is removed under reduced pressure and the product is purified by preparative HPLC. This gives 0.086 g (87% of theory) of the product.

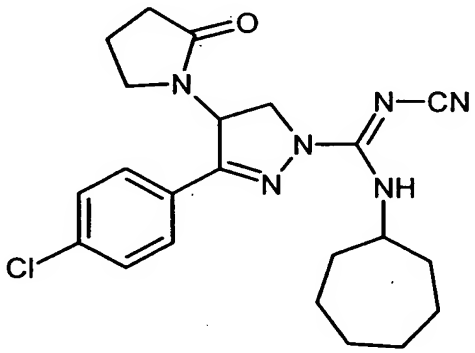
LC-MS (method 14): R_t = 2.4 min.

MS (ESI pos): m/z = 401 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.88 (t, 3H), 1.30 (m, 4H), 1.57 (m, 2H), 1.77 (m, 1H), 1.89 (m, 1H), 2.22 (m, 2H), 2.76 (m, 1H), 3.25 (m, 1H), 3.38 (m, 2H), 4.19 (m, 2H), 6.01 (dd, 1H), 7.57 (d, 2H), 7.77 (d, 2H), 7.95 (t, 1H).

Example 150

3-(4-Chlorophenyl)-*N'*-cyano-*N*-cycloheptyl-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.055 g (0.49 mmol) of heptylamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.09 g (85% of theory) of the product.

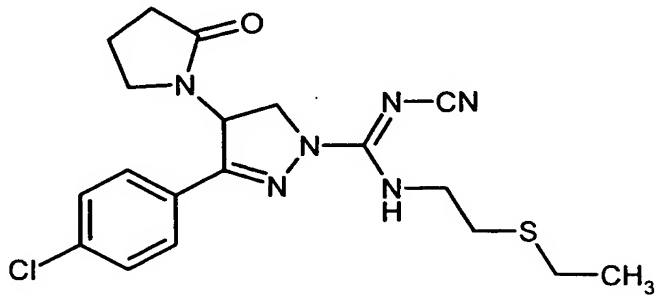
LC-MS (method 14): R_t = 2.55 min.

MS (ESI pos): m/z = 427 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.51-1.66 (m, 11H), 1.89 (m, 3H), 2.26 (m, 2H), 2.77 (m, 1H), 3.25 (m, 1H), 4.07 (m, 1H), 4.20 (m, 2H), 6.01 (dd, 1H), 7.49 (d, 1H), 7.56 (d, 2H), 7.79 (d, 2H).

Example 151

3-(4-Chlorophenyl)-*N'*-cyano-*N*-[2-(ethylthio)ethyl]-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl-3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.069 g (0.49 mmol) of 2-(ethylmercapto)ethylamine hydrochloride are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.077 g (74% of theory) of the product.

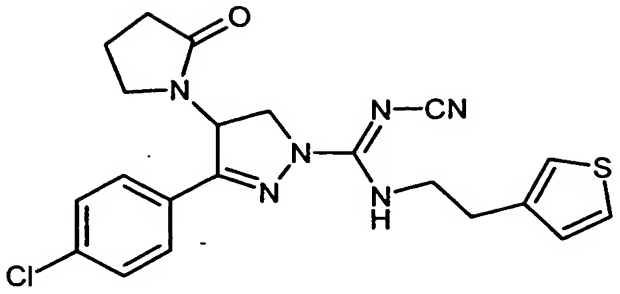
LC-MS (method 14): R_t = 2.18 min.

MS (ESI pos): m/z = 419 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.20 (t, 3H), 1.75 (m, 1H), 1.91 (m, 1H), 2.22 (m, 2H), 2.56 (q, 2H), 2.71 (m, 3H), 3.29 (m, 1H), 3.54 (m, 2H), 4.23 (m, 2H), 6.04 (dd, 1H), 7.58 (d, 2H), 7.77 (d, 2H), 8.08 (t, 1H).

Example 152

3-(4-Chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-[2-(3-thienyl)ethyl]-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.062 g (0.49 mmol) of 2-(3-thienyl)ethanamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.069 g (64% of theory) of the product.

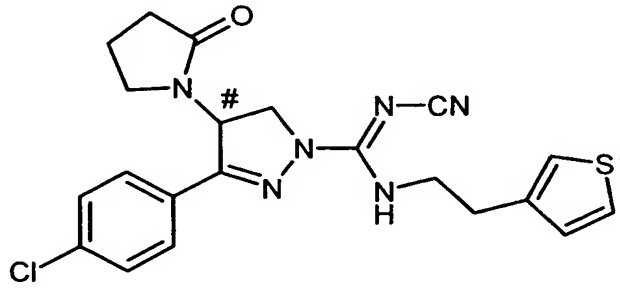
LC-MS (method 13): R_t = 2.44 min.

MS (ESI pos): m/z = 441 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.77 (m, 1H), 1.89 (m, 1H), 2.23 (m, 2H), 2.76 (m, 1H), 3.11 (m, 2H), 3.27 (m, 1H), 3.63 (m, 2H), 4.22 (m, 2H), 6.04 (dd, 1H), 6.95 (m, 2H), 7.34 (dd, 1H), 7.58 (d, 2H), 7.76 (d, 2H), 8.06 (t, 1H).

Example 153

3-(4-Chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-[2-(3-thienyl)ethyl]-4,5-dihydro-1H-pyrazole-1-carboximidamide

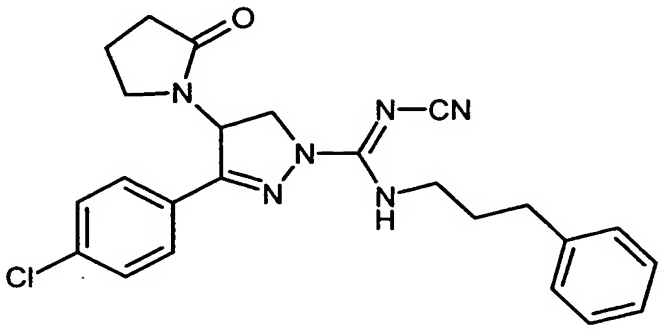


Separation of the enantiomers of Example 152 by method 18 gives the title compound as enantiomer 2 (>98.9% ee).

HPLC (method 18): R_t = 10.87 min. (second fraction)

Example 154

3-(4-Chlorophenyl)-*N*'-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-(3-phenylpropyl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.066 g (0.49 mmol) of 3-phenylpropan-1-amine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.094 g (85% of theory) of the product.

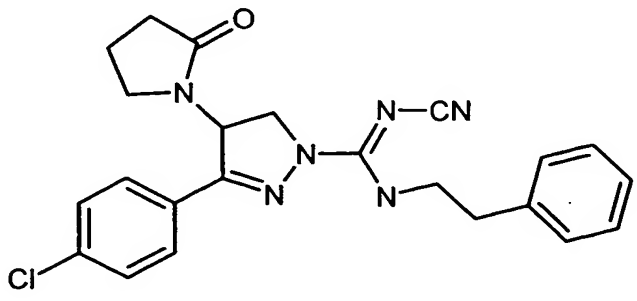
LC-MS (method 13): $R_t = 2.59$ min.

MS (ESI pos): $m/z = 449$ $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.90 (m, 2H), 2.02 (t, 2H), 2.36 (m, 2H), 2.74 (t, 2H), 2.87 (m, 1H), 3.34 (m, 1H), 3.59 (m, 2H), 4.16 (dd, 1H), 4.40 (dd, 1H), 6.15 (dd, 1H), 6.30 (t, 1H), 7.22 (m, 5H), 7.41 (d, 2H), 7.64 (d, 2H).

Example 155

3-(4-Chlorophenyl)-*N*'-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.059 g (0.49 mmol) of 2-phenylethanamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added to the reaction mixture, whereupon the product crystallizes as a solid. The product is filtered off with suction and washed repeatedly with diethyl ether. Drying under high vacuum gives 0.080 g (75% of theory) of the product.

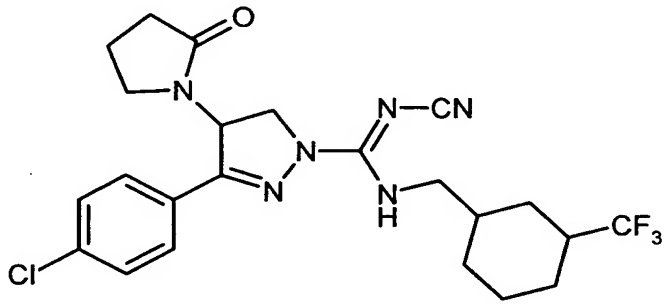
LC-MS (method 14): R_t = 2.33 min.

MS (ESI pos): m/z = 435 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.76 (m, 1H), 1.89 (m, 1H), 2.22 (m, 2H), 2.75 (m, 1H), 2.89 (t, 2H), 3.26 (m, 1H), 3.61 (m, 2H), 4.18 (m, 2H), 6.02 (dd, 1H), 7.28 (m, 5H), 7.58 (m, 2H), 7.76 (d, 2H), 8.03 (t, 1H).

Example 156

3-(4-Chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-{[3-(trifluoromethyl)cyclohexyl]methyl}-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl-3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.053 g (0.29 mmol) of 1-[3-(trifluoromethyl)cyclohexyl]-methanamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the solvent is removed under reduced pressure and the product is purified by preparative HPLC. This gives 0.103 g (85% of theory) of the product.

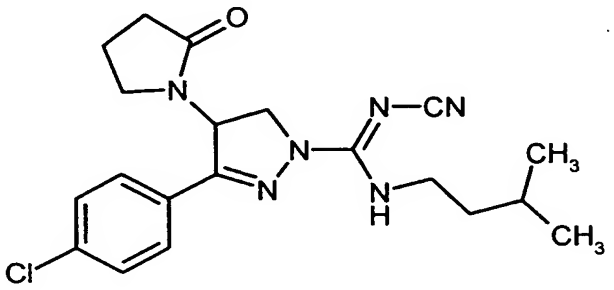
LC-MS (method 14): R_t = 2.7 min.

MS (ESI pos): m/z = 495 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.90 (m, 2H), 1.23 (m, 2H), 1.49 (m, 1H), 1.77 (m, 6H), 2.25 (m, 3H), 2.76 (m, 1H), 3.27 (m, 3H), 4.20 (m, 2H), 6.02 (dd, 1H), 7.59 (d, 2H), 7.77 (d, 2H), 8.08 (t, 1H).

Example 157

3-(4-Chlorophenyl)-*N'*-cyano-*N*-(3-methylbutyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.042 g (0.49 mmol) of 3-methylbutan-1-amine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the solvent is removed under reduced pressure and the product is purified by preparative HPLC. This gives 0.087 g (88% of theory) of the product.

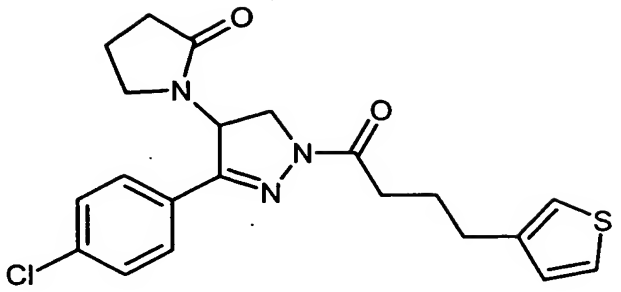
LC-MS (method 14): R_t = 2.38 min.

MS (ESI pos): m/z = 401 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.92 (d, 6H), 1.48 (m, 2H), 1.61 (m, 1H), 1.77 (m, 1H), 1.89 (m, 1H), 2.22 (m, 2H), 2.76 (m, 1H), 3.25 (m, 1H), 3.37 (m, 2H), 4.19 (m, 2H), 6.01 (dd, 1H), 7.56 (d, 2H), 7.77 (d, 2H), 7.92 (t, 1H).

Example 158

1-{3-(4-Chlorophenyl)-1-[4-(3-thienyl)butanoyl]-4,5-dihydro-1H-pyrazol-4-yl}pyrrolidin-2-one



0.1 g (0.379 mmol) of 1-[3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one, 0.064 g (0.379 mmol) of 4-(3-thienyl)butanoic acid, 5 mg (0.038 mmol) of dimethylaminopyridine, 0.145 g (0.758 mmol) of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, 0.05 g (0.379 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 0.16 ml (1.138 mmol) of triethylamine are stirred in 2 ml of anhydrous tetrahydrofuran overnight. The salts are filtered off, the solvent is then removed under reduced pressure and the residue that remains is purified by preparative HPLC. This gives 0.1 g (65% of theory) of the product.

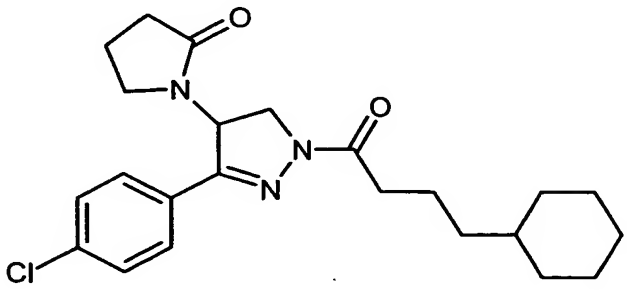
LC-MS (method 14): R_t = 2.50 min.

MS (ESI pos): m/z = 416 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.91 (m, 3H), 2.18 (m, 2H), 2.66 (m, 7H), 3.96 (m, 2H), 5.94 (t, 1H), 6.99 (dd, 1H), 7.17 (dd, 1H), 7.46 (dd, 1H), 7.56 (d, 2H), 7.63 (d, 2H).

Example 159

1-[3-(4-Chlorophenyl)-1-(4-cyclohexylbutanoyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one



0.1 g (0.379 mmol) of 1-[3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]pyrrolidin-2-one, 0.064 g (0.379 mmol) of 4-cyclohexylbutyric acid, 5 mg (0.038 mmol) of dimethylaminopyridine, 0.145 g (0.758 mmol) of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, 0.05 g (0.379 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 0.16 ml (1.138 mmol) of triethylamine are stirred in 2 ml of anhydrous tetrahydrofuran overnight. The salts are filtered off, the solvent is

then removed under reduced pressure and the residue that remains is purified by preparative HPLC. This gives 0.077 g (49% of theory) of the product.

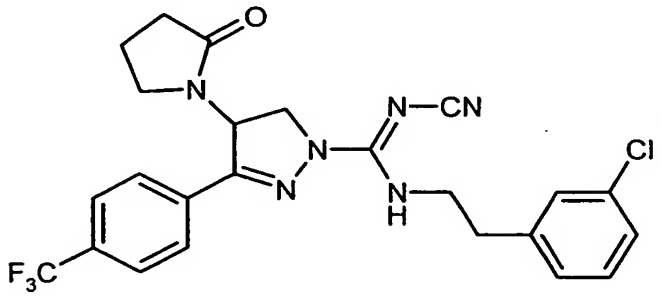
LC-MS (method 14): R_t = 3.1 min.

MS (ESI pos): m/z = 416 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.86 (m, 2H), 1.22 (m, 6H), 1.63 (m, 8H), 1.89 (m, 1H), 2.23 (m, 2H), 2.71 (m, 3H), 3.26 (m, 1H), 3.96 (m, 2H), 5.94 (dd, 1H), 7.51 (d, 2H), 7.66 (d, 2H).

Example 160

3-(4-Trifluoromethyl)-*N*'-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-[2-(3-chlorophenyl)ethyl]-4,5-dihydro-1H-pyrazole-1-carboximidamide



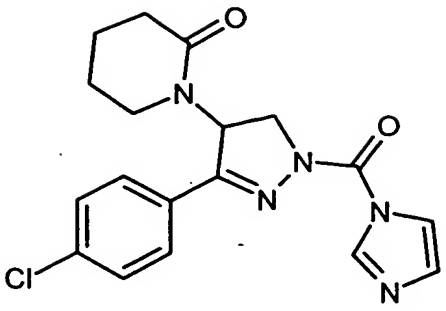
50 mg (0.113 mmol) of phenyl-3-(4-trifluoromethylphenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 35 mg (0.227 mmol) of 2-(3-chlorophenyl)ethanamine are dissolved in 2 ml of DMF and heated at 100°C overnight. The product is purified by RP-HPLC. This gives 44 mg (77% of theory) of the product.

LC-MS (method 4): R_t = 2.29 min.

MS (ESI pos): m/z = 503 $(M+H)^+$

Example 161

1-[3-(4-Chlorophenyl)-1-(1H-imidazol-1-ylcarbonyl)-4,5-dihydro-1H-pyrazol-4-yl]piperidin-2-one



At 0-5°C, over a period of 30 min, 200 mg (0.72 mmol) of 1-[3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-4-yl]piperidin-2-one (preparation analogously to Example XII) are added in 4 portions to a solution of 140 mg (0.86 mmol) of carbonyldiimidazole in 1 ml of anhydrous THF, and the mixture is stirred at this temperature for 45 minutes. The resulting precipitate is filtered off, washed with methyl *tert*-butyl ether and dried under reduced pressure.

Yield: 138 mg (52% of theory) of a solid

Concentration of the mother liquid and chromatography on silica gel (dichloromethane/methanol 40:1) yields a further 114 mg (43% of theory) of product.

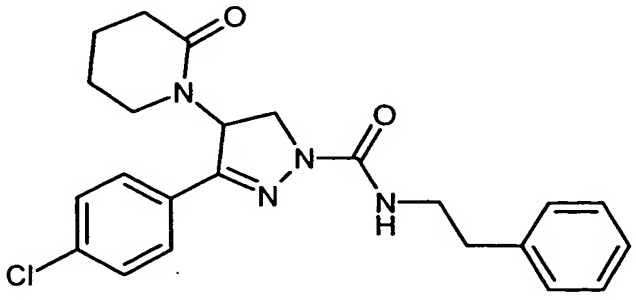
LC-MS (method 13): R_t = 1.80 min.

MS (ESI pos): m/z = 372 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.5 (m, 2H), 1.7 (m, 2H), 2.25 (t, 2H), 2.82 (m, 1H), 3.3 (m, 1H), 4.13 (dd, 1H), 4.32 (dd, 1H), 6.43 (m, 1H), 7.1 (m, 1H), 7.59 (m, 2H), 7.75 (m, 2H), 7.87 (m, 1H), 8.52 (m, 1H)

Example 162

3-(4-Chlorophenyl)-4-(2-oxopiperidin-1-yl)-*N*-(2-phenylethyl)-4,5-dihydro-1H-pyrazole-1-carboxamide



At room temperature, 13 mg (0.11 mmol) of phenethylamine are added to a solution of 40 mg (0.11 mmol) of the compound from Example 161 in 0.5 ml of THF and the mixture is stirred at RT overnight. The mixture is partitioned between in each case 50 ml of ethyl acetate and saturated sodium chloride solution comprising 1 ml of 1M acetic acid, and the organic phase is washed again with saturated sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure.

Yield: 46 mg (89% of theory)

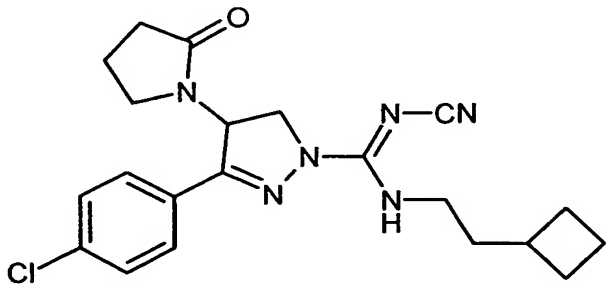
LC-MS (method 13): R_t = 2.52 min.

MS (ESI pos): m/z = 425 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.5 (m, 2H), 1.7 (m, 2H), 2.25 (t, 2H), 2.63 (m, 1H), 2.7 (m, 2H), 3.1 (m, 1H), 3.34 (m, 2H), 3.35 (dd, 1H), 4.0 (dd, 1H), 6.43 (m, 1H), 7.25 (m, 5H), 7.59 (m, 2H), 7.52 (m, 2H), 7.72 (m, 2H), 8.52

Example 163

3-(4-Chlorophenyl)-*N*^{c}-cyano-*N*-(2-cyclobutylethyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.28 ml (2.02 mmol) of triethylamine is added to a solution of 274 mg (0.67 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 100 mg (1.01 mmol) of 2-cyclobutylethylamine in 3 ml of DMF, and the mixture is stirred at 70°C for 24 h. The solution is then concentrated under reduced pressure, water and saturated sodium chloride solution are added and the mixture is extracted with dichloromethane. The organic phase is dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue is purified by preparative HPLC. This gives 79 mg (28% of theory) of the product.

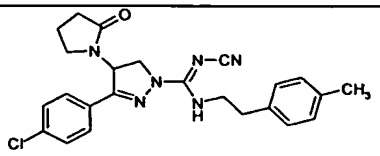
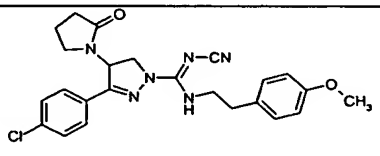
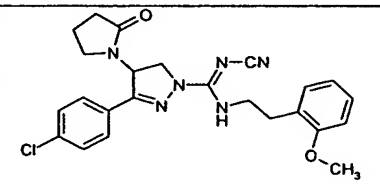
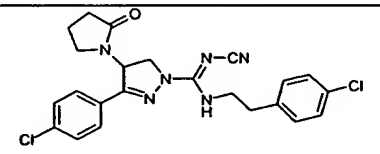
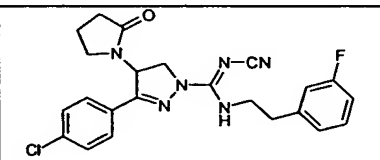
LC-MS (method 14): R_t = 2.43 min.

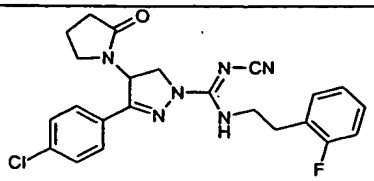
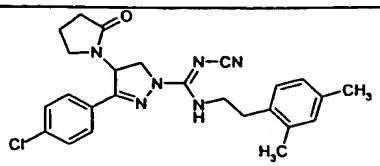
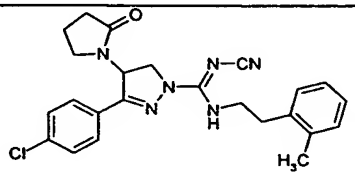
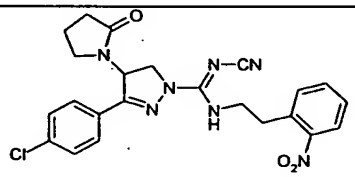
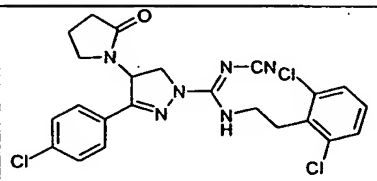
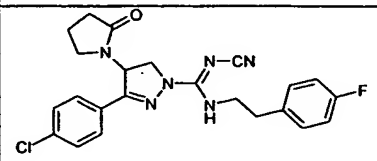
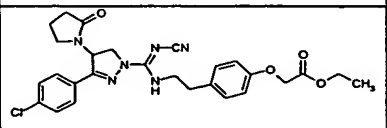
MS (ESI pos): m/z = 413 $(M+H)^+$,

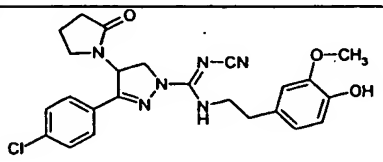
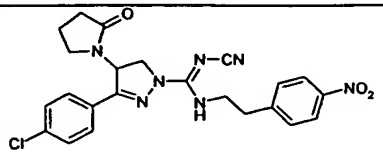
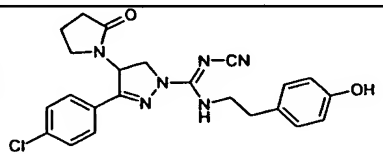
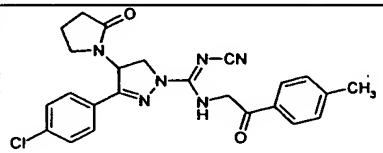
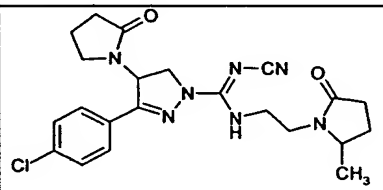
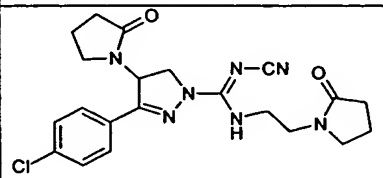
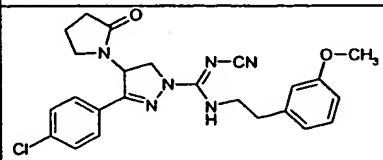
MS (ESI neg): m/z = 411 $(M-H)^-$

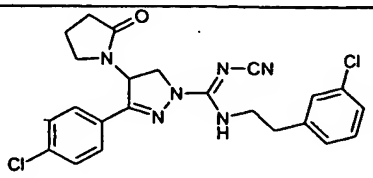
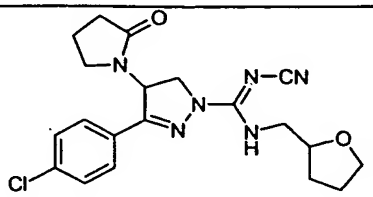
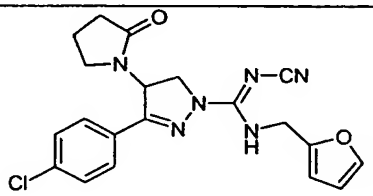
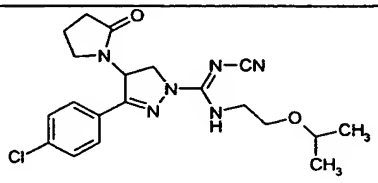
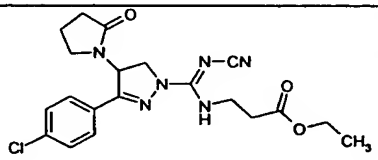
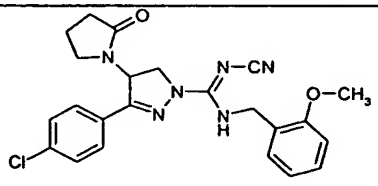
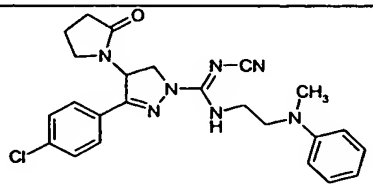
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.55-1.98 (m, 9H), 1.98-2.1 (m, 2H), 2.12-2.38 (m, 3H), 2.75 (dt, 1H), 3.25-3.4 (m, 2H), 4.15-4.28 (m, 2H), 6.0 (dd, 1H), 7.55 (d, 2H), 7.79 (d, 2H), 7.9 (t, 1H).

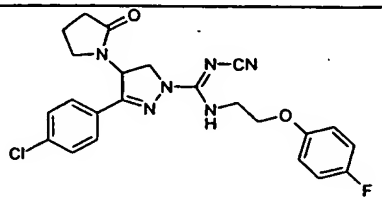
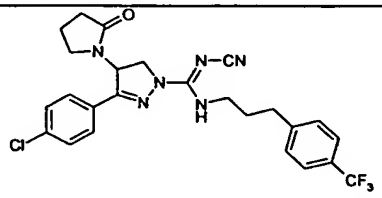
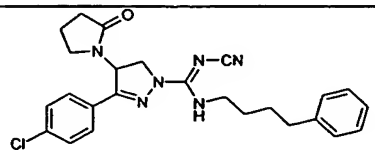
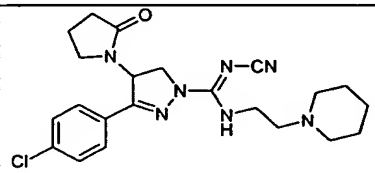
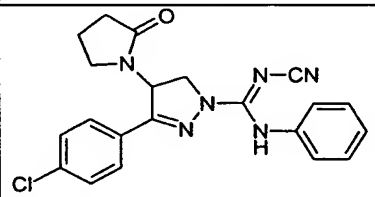
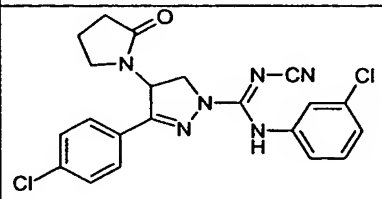
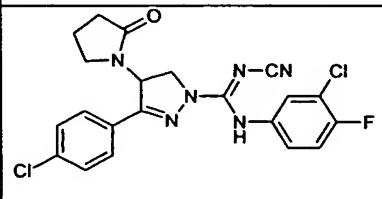
The compounds of Examples 164 to 404 are prepared analogously to the Examples described.

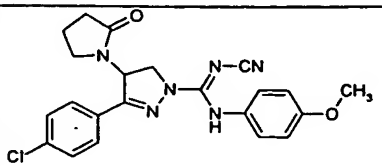
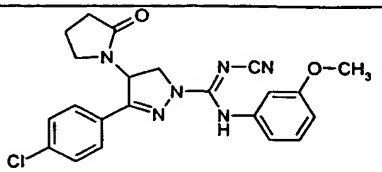
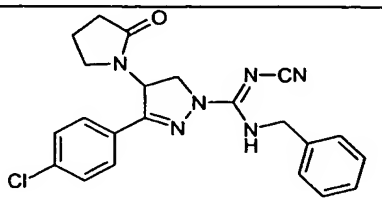
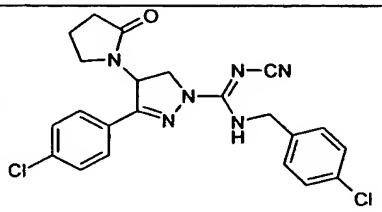
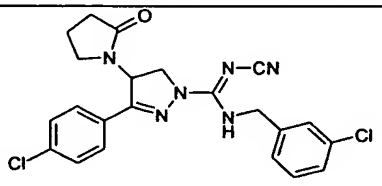
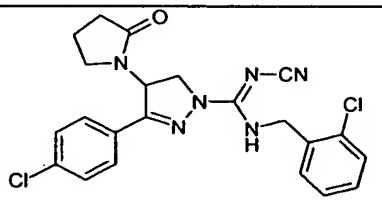
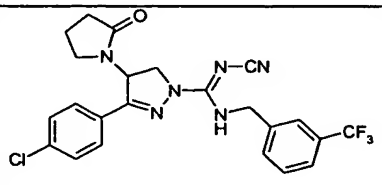
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
164		449	2.43	14
165		465	2.29	14
166		465	2.54	14
167		469	2.45	14
168		453	2.48	15

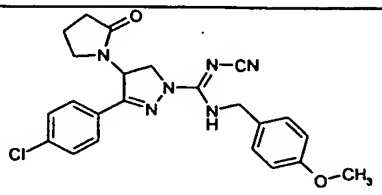
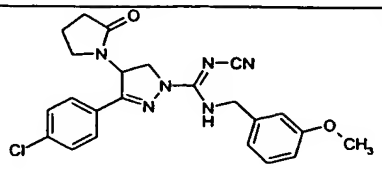
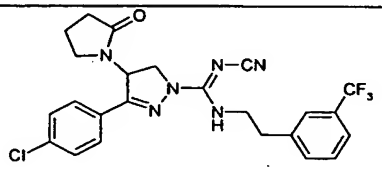
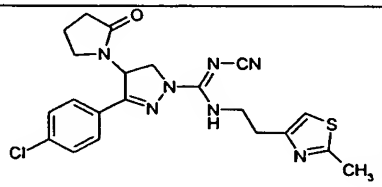
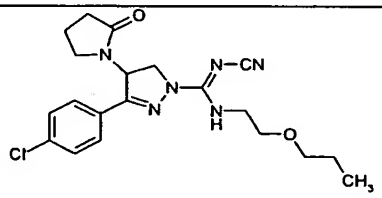
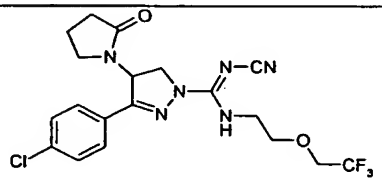
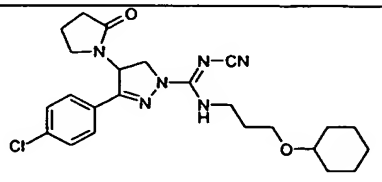
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
169		453	2.32	14
170		463	2.7	15
171		449	2.59	13
172		480	2.43	13
173		503	2.69	13
174		453	2.5	13
175		537	2.42	13

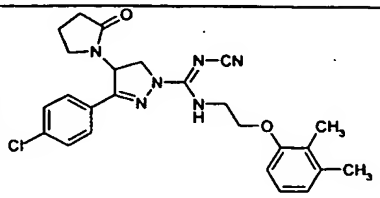
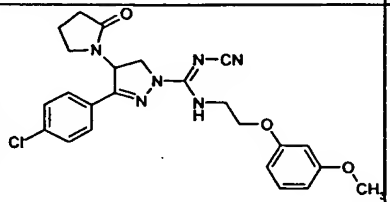
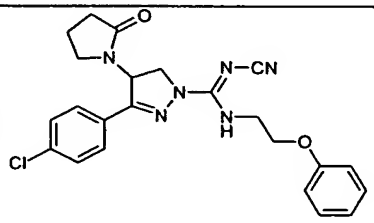
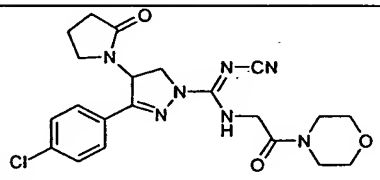
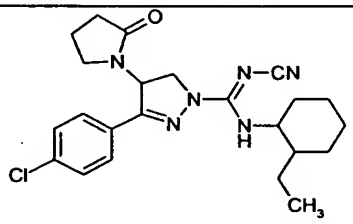
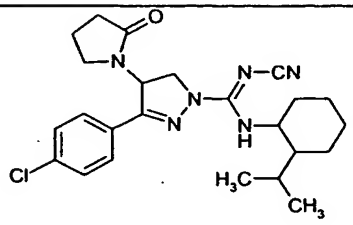
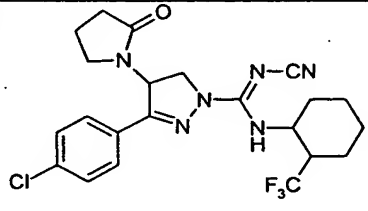
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
176		481	2.17	13
177		480	2.44	13
178		451	2.15	13
179		463	2.3	13
180		456	1.97	13
181		442	1.84	13
182		465	2.3	14

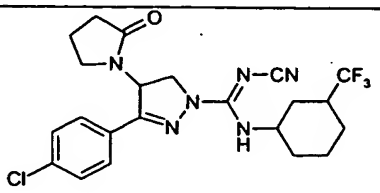
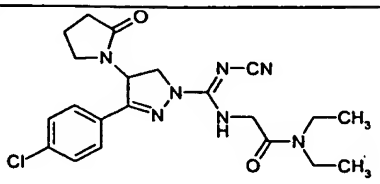
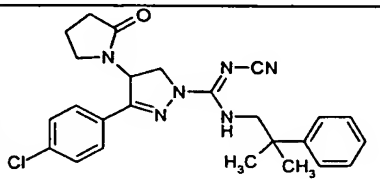
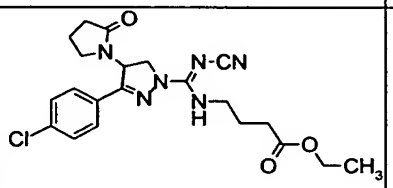
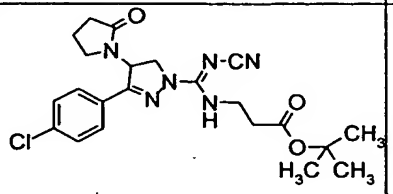
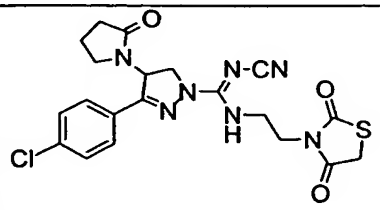
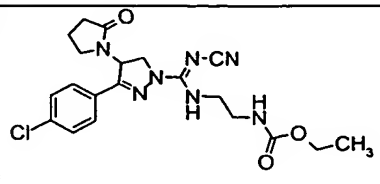
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
183		469	2.43	13
184		415	2.06	13
185		411	2.18	13
186		417	2.29	13
187		431	2.0	14
188		451	2.46	13
189		464	2.5	13

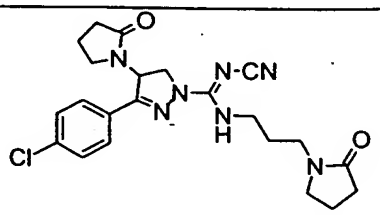
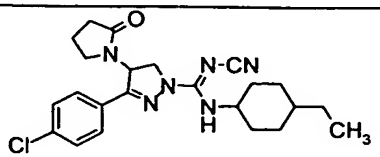
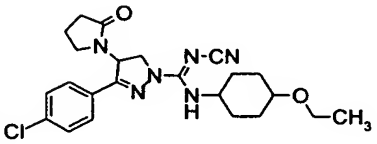
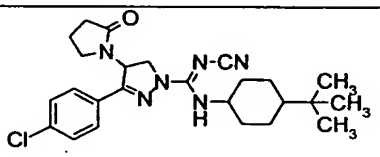
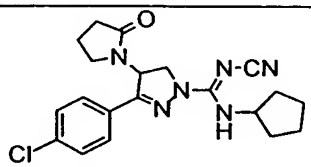
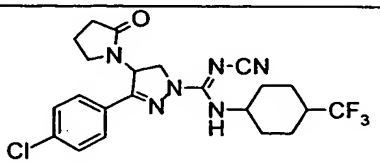
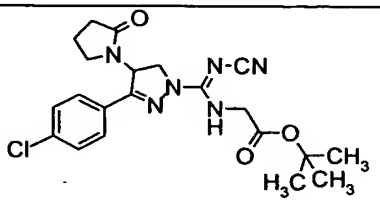
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
190		469	2.42	13
191		517	2.7	13
192		463	2.63	13
193		442	1.67	13
194		407	2.09	14
195		441	2.41	13
196		459	2.42	13

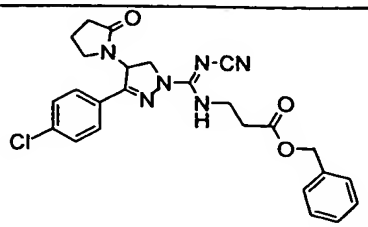
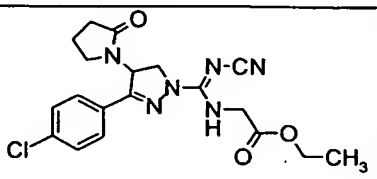
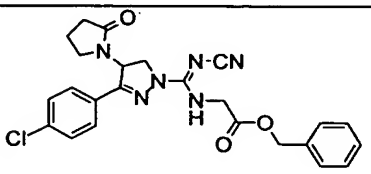
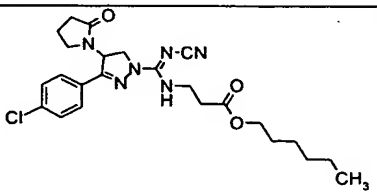
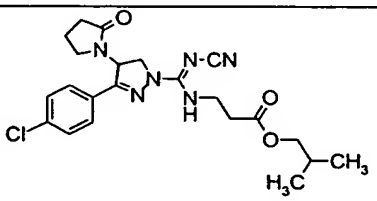
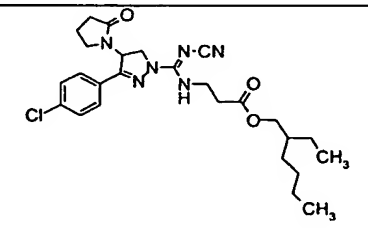
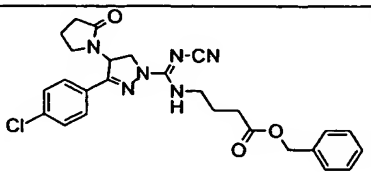
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
197		437	2.22	13
198		437	2.13	14
199		421	2.22	14
200		455	2.47	14
201		455	2.46	13
202		455	2.45	13
203		489	2.52	13

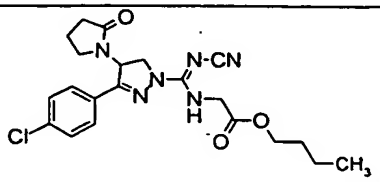
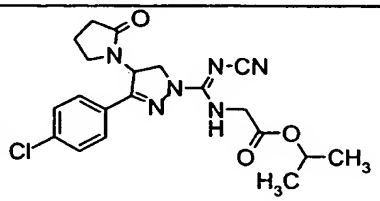
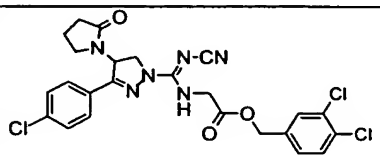
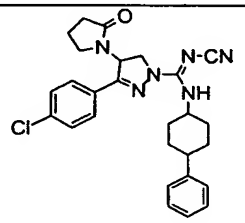
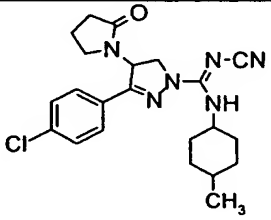
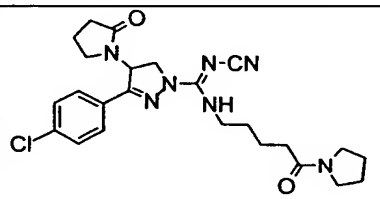
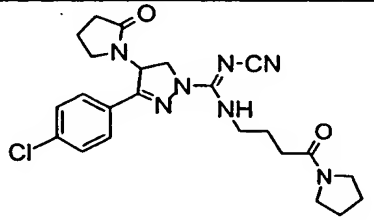
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
204		451	2.32	13
205		451	2.33	13
206		503	2.48	14
207		456	2.12	13
208		417	2.17	14
209		457	2.3	13
210		471	2.66	13

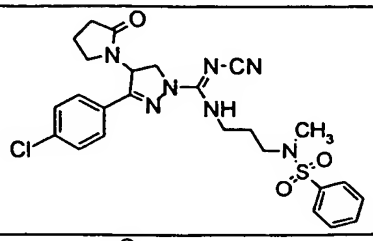
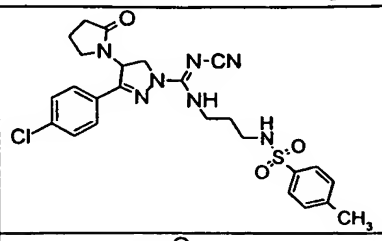
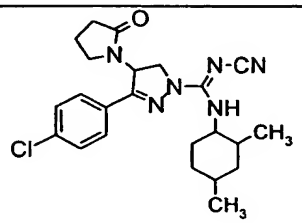
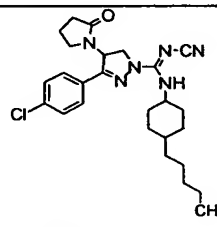
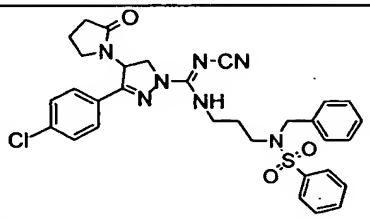
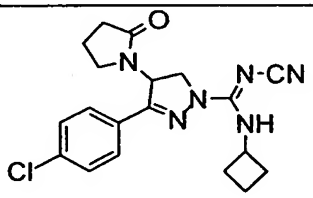
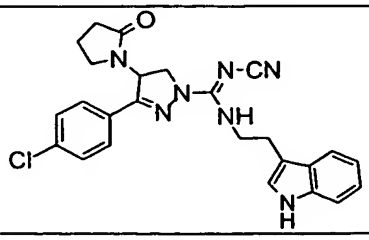
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
211		479	2.67	13
212		481	2.3	13
213		451	2.44	13
214		458	1.87	13
215		441	3.16	13
216		455	2.71	14
217		481	3.06	13

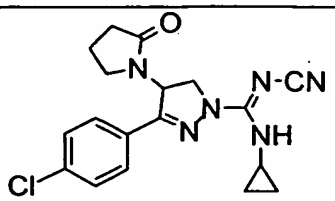
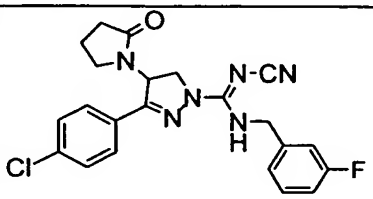
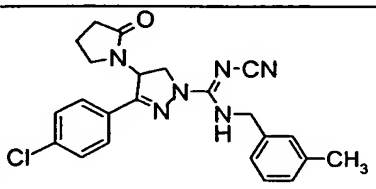
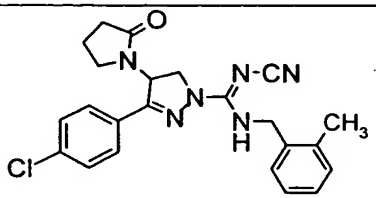
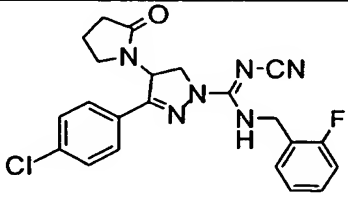
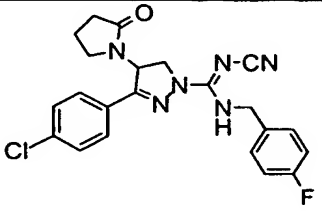
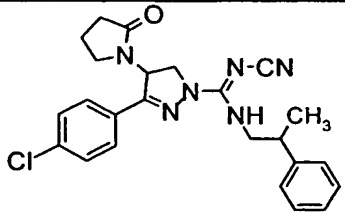
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
218		481	2.65	13
219		444	2.15	15
220		463	2.48	14
221		445	2.02	14
222		459	2.45	15
223		474	1.79	14
224		446	2.06	15

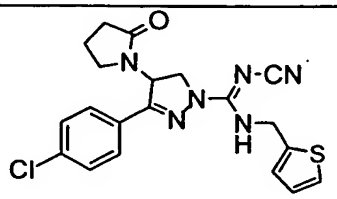
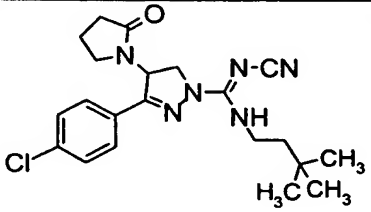
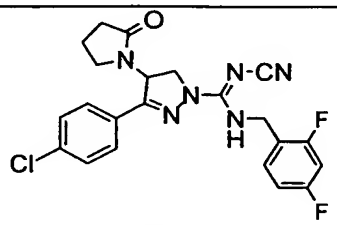
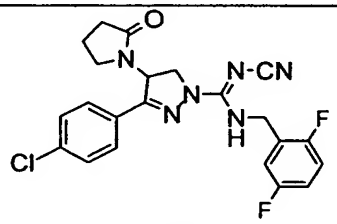
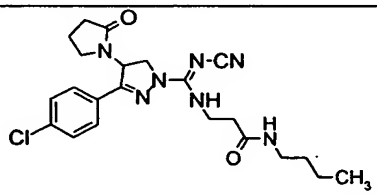
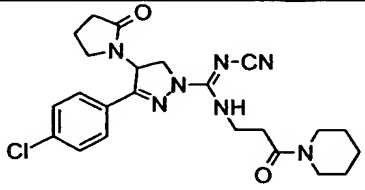
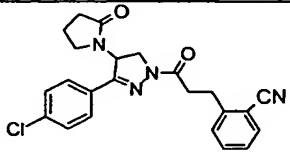
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
225		456	1.69	14
226		441	2.81	13
227		457	2.33	13
228		469	2.85	14
229		399	2.2	14
230		481	2.38	14
231		445	2.38	15

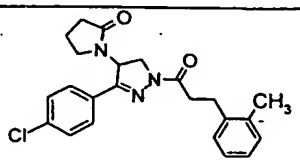
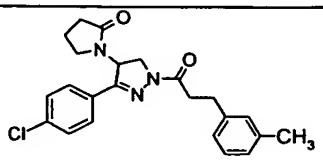
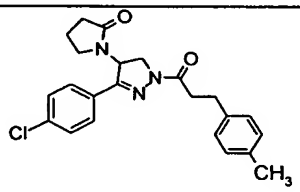
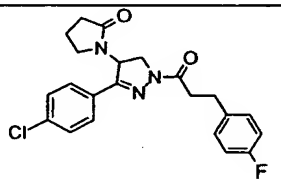
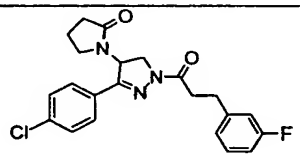
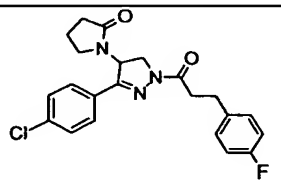
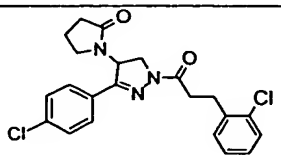
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
232		493	2.23	14
233		417	1.88	14
234		479	2.17	14
235		487	2.53	14
236		459	2.23	14
237		515	2.77	14
238		507	2.29	14

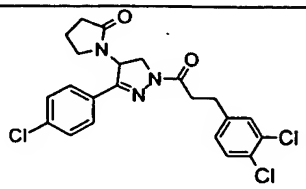
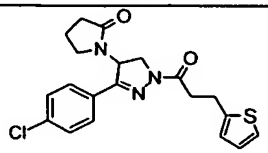
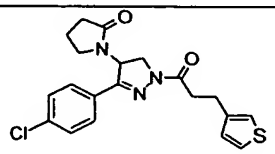
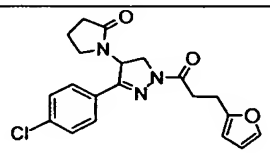
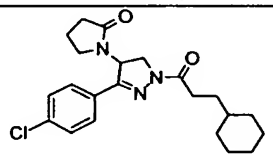
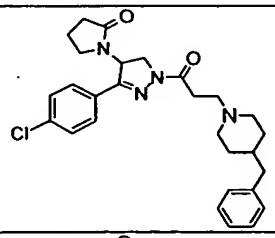
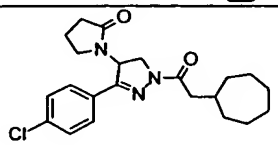
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
239		445	2.37	13
240		431	2.01	14
241		547	2.43	14
242		489	2.69	14
243		427	2.69	13
244		484	2.10	15
245		470	2.04	15

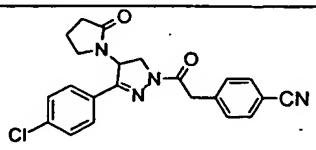
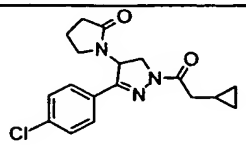
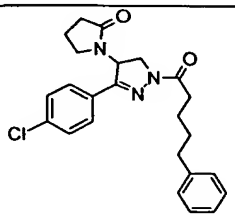
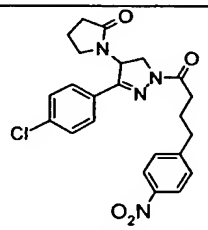
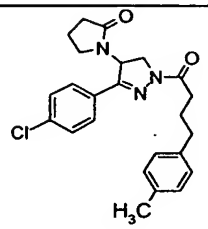
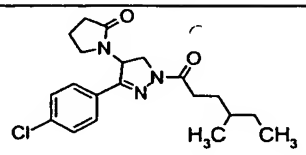
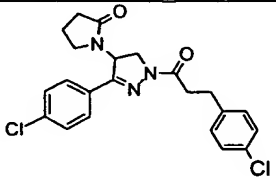
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
246		542	2.39	13
247		542	2.32	13
248		441	2.94	16
249		483	3.12	14
250		618	2.58	14
251		385	2.17	14
252		474	2.51	13

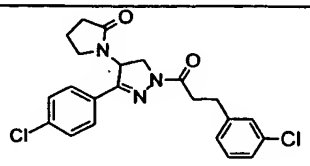
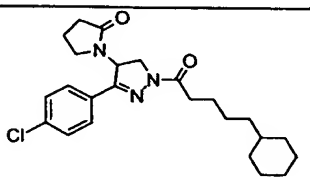
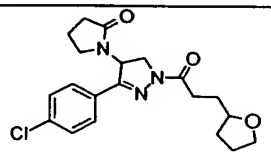
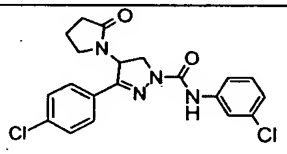
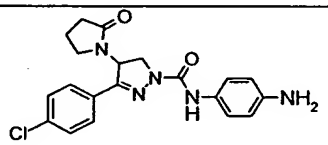
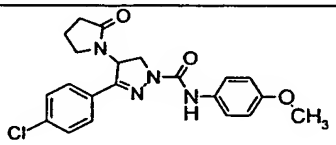
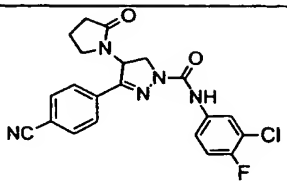
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
253		371	2.18	13
254		439	2.26	14
255		435	2.35	14
256		435	2.58	13
257		439	2.25	14
258		439	2.26	14
259		449	2.43	14

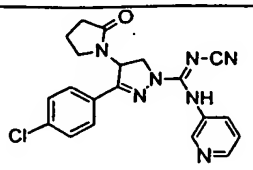
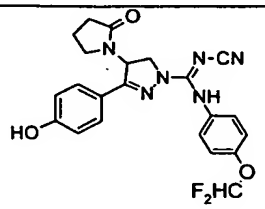
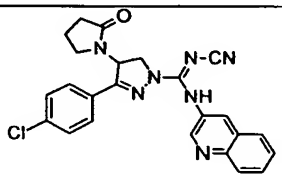
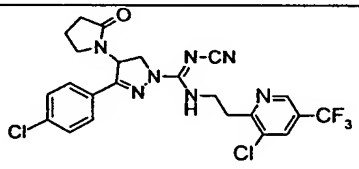
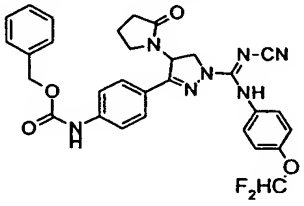
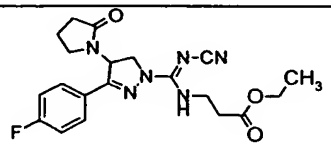
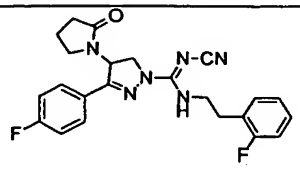
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
260		427	2.18	14
261		415	2.48	14
262		457	2.30	14
263		457	2.27	14
264		459	1.89	4
265		471	1.92	4
266		421	2.48	13

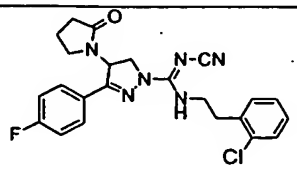
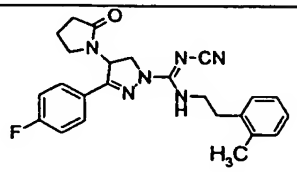
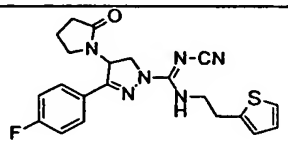
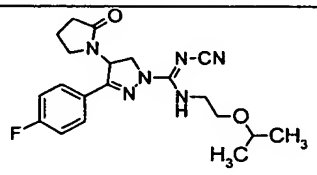
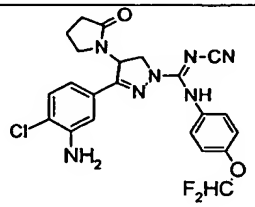
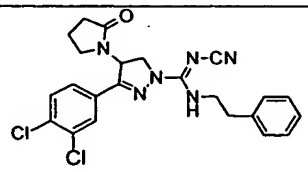
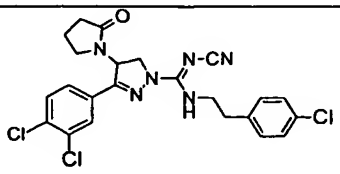
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
267		410	2.74	13
268		410	2.76	13
269		410	2.77	13
270		414	2.65	13
271		414	2.64	13
272		414	2.63	13
273		430	2.80	13

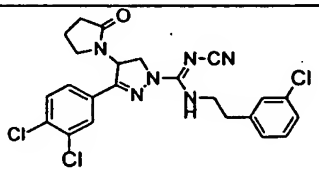
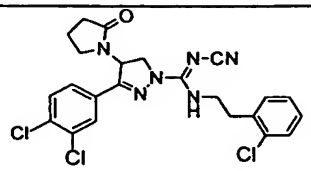
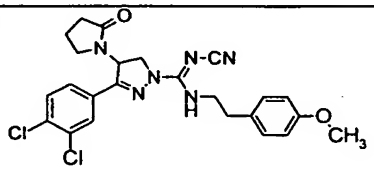
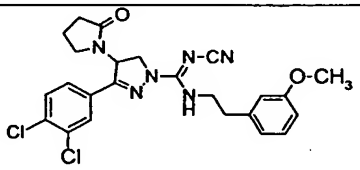
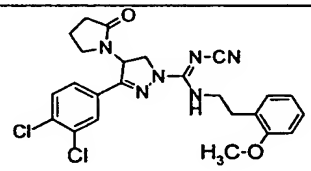
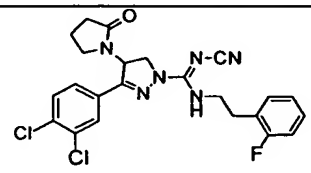
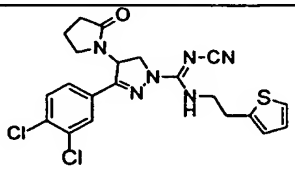
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
274		463	2.93	13
275		402	2.58	13
276		402	2.56	13
277		386	2.28	13
278		402	3.10	13
279		493	1.84	13
280		402	3.05	13

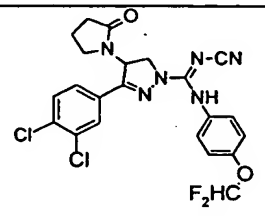
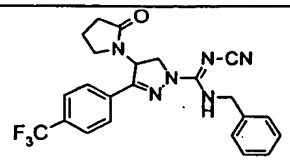
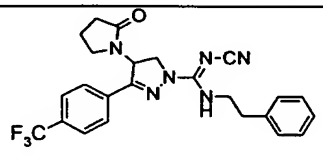
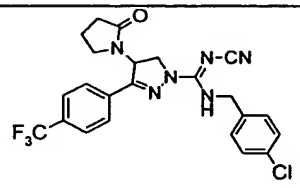
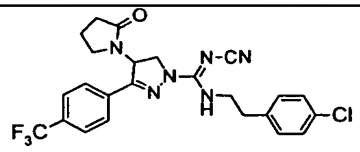
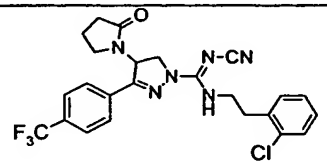
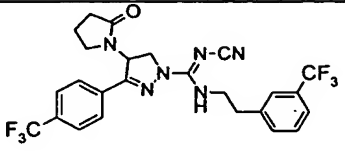
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
281		407	2.38	13
282		346	2.39	13
283		424	2.88	13
284		455	2.65	13
285		424	2.90	13
286		376	2.68	13
287		430	2.60	14

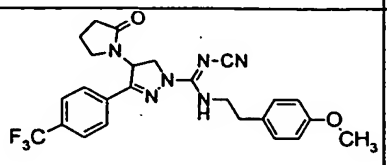
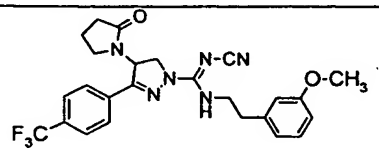
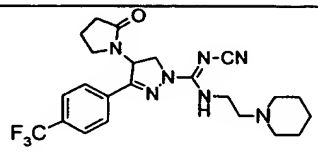
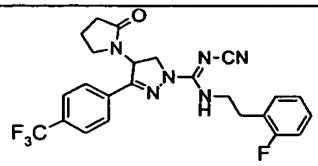
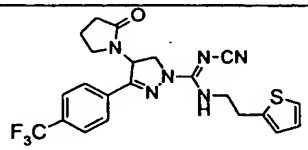
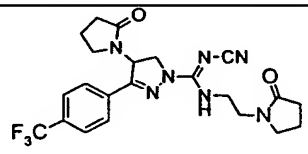
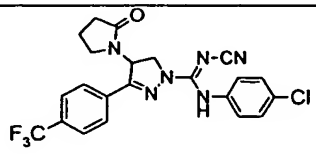
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
288		430	2.69	13
289		430	3.23	14
290		390	2.18	13
291		417	2.70	13
292		398	1.55	13
293		413	2.35	13
294		426	2.29	14

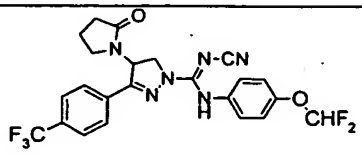
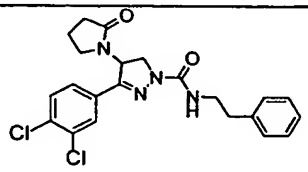
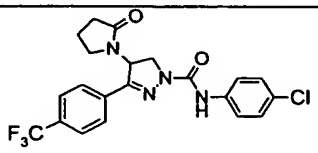
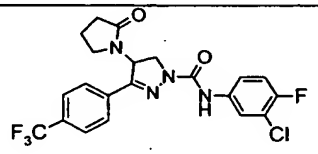
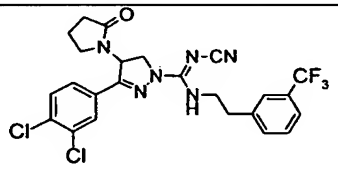
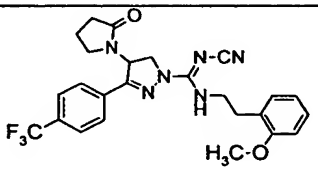
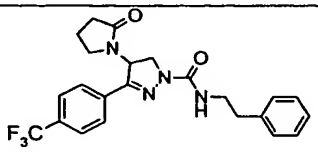
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
295		408	1.63	14
296		455	1.98	13
297		458	2.14	13
298		538	2.24	4
299		588	2.30	14
300		415	1.85	4
301		437	2.07	4

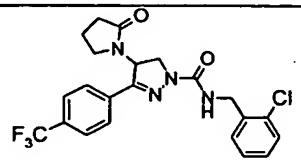
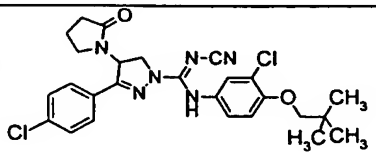
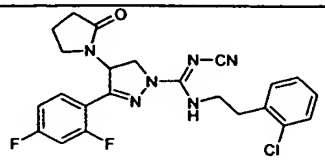
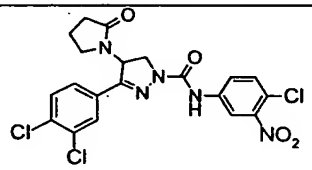
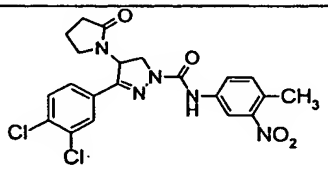
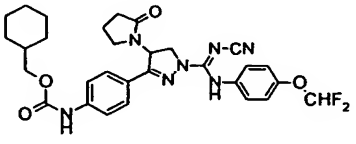
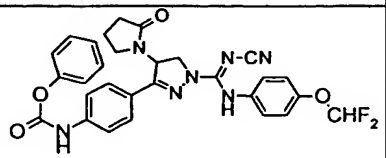
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
302		453	2.16	4
303		433	2.14	4
304		425	2.03	4
305		401	1.91	4
306		488	2.07	14
307		469	2.28	4
308		503	2.36	4

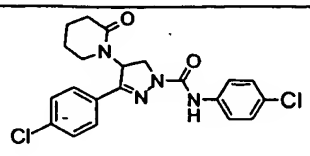
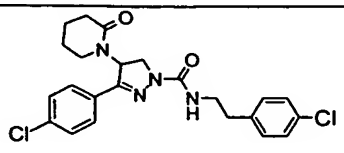
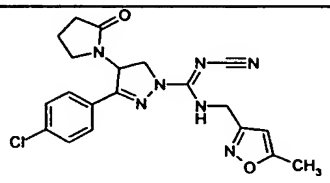
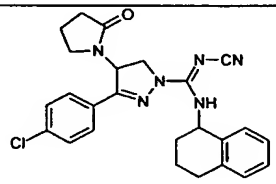
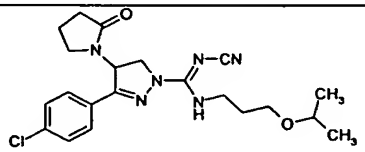
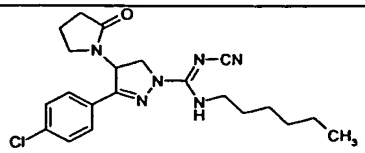
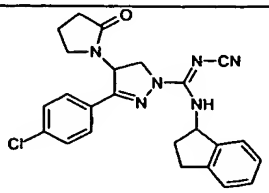
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
309		503	2.35	4
310		503	2.36	4
311		499	2.23	4
312		499	2.27	4
313		499	2.31	4
314		487	2.27	4
315		475	2.24	4

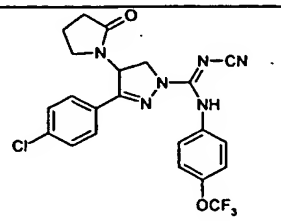
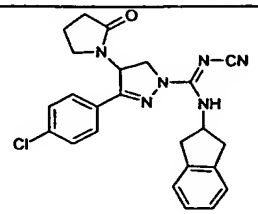
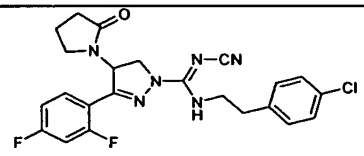
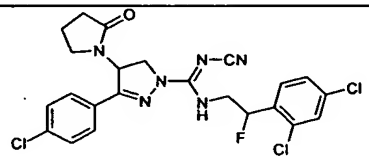
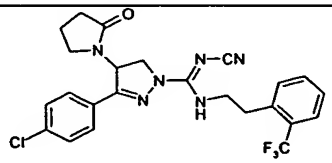
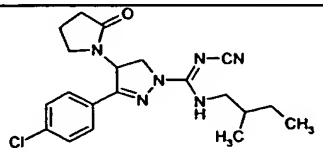
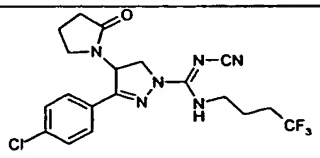
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
316		507	2.18	4
317		455	2.12	4
318		469	2.19	4
319		499	2.23	4
320		503	2.29	4
321		503	2.28	4
322		537	2.29	4

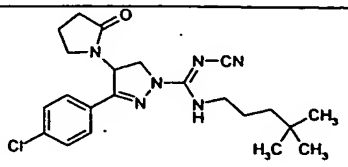
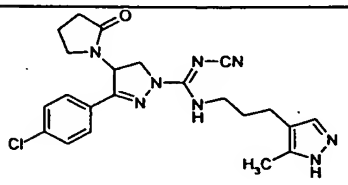
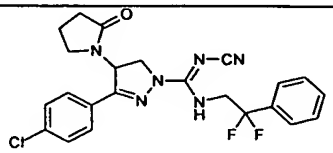
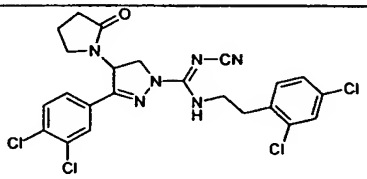
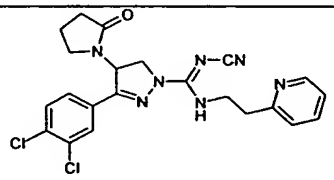
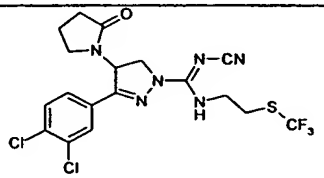
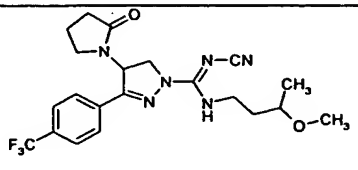
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
323		499	2.18	4
324		499	2.19	4
325		476	1.38	4
326		487	2.19	4
327		475	2.14	4
328		476	1.78	4
329		475	2.18	4

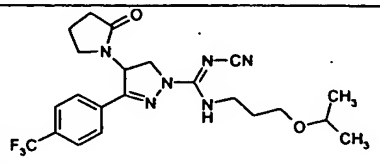
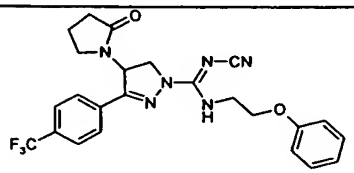
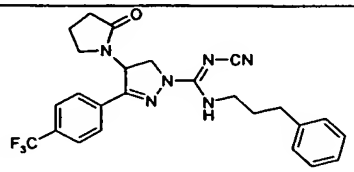
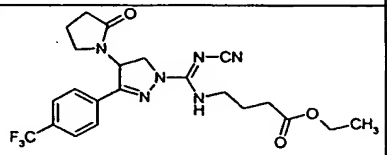
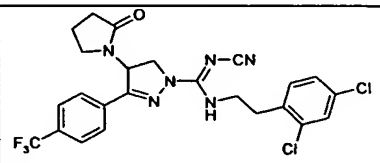
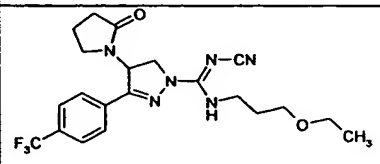
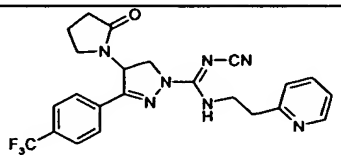
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
330		507	2.13	4
331		445	2.30	4
332		451	2.34	4
333		469	2.57	14
334		537	2.60	14
335		499	2.21	4
336		445	2.38	14

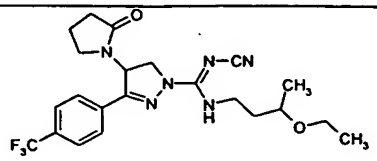
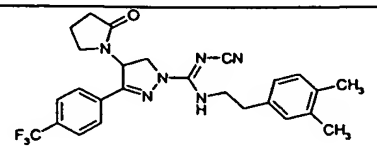
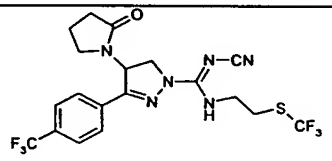
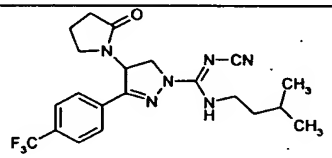
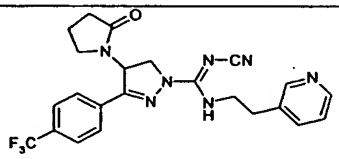
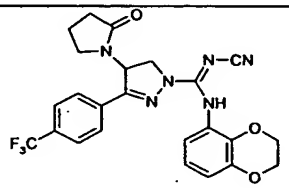
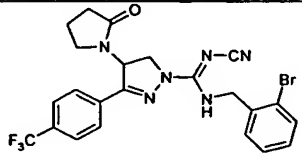
Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
337		465	2.45	14
338		527	2.44	4
339		471	2.44	13
340		496	2.42	4
341		476	2.39	4
342		594	2.34	4
343		574	2.09	4

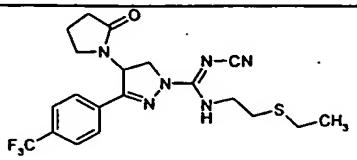
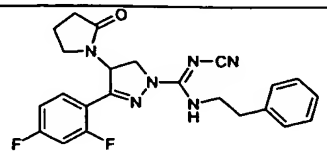
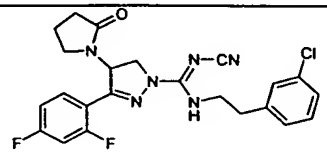
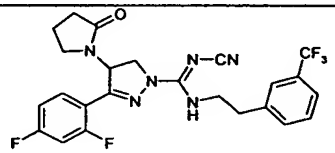
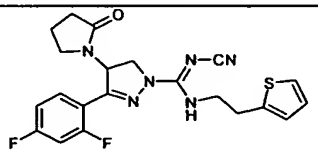
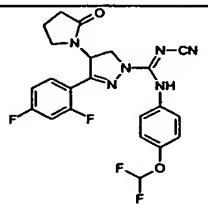
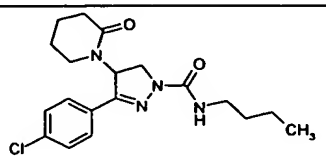
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
344		431	2.79	15
345		459	2.77	15
346		425	2.14	13
347		461	2.67	13
348		431	2.35	13
349		429	2.83	13
350		447	2.62	13

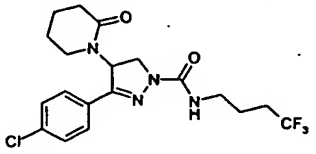
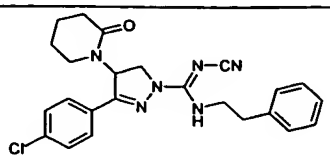
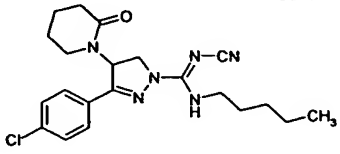
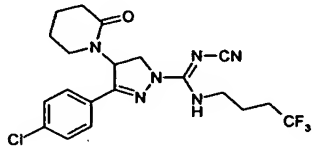
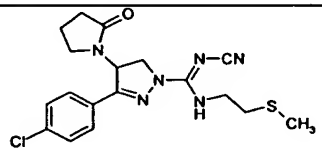
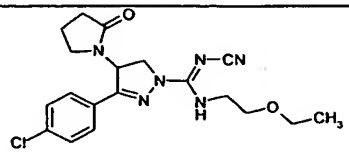
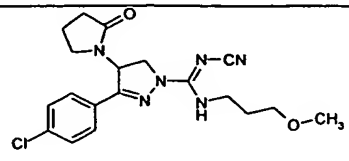
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
351		491	2.58	13
352		447	2.39	14
353		471	2.32	14
354		521	2.53	14
355		503	2.49	14
356		401	2.33	14
357		441	2.20	14

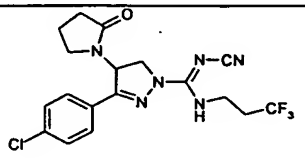
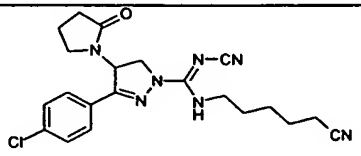
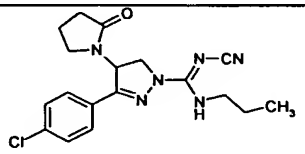
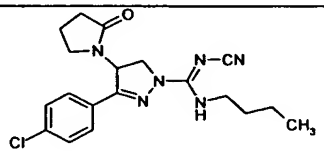
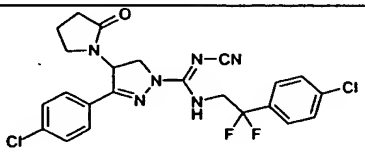
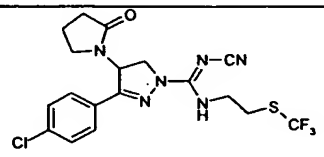
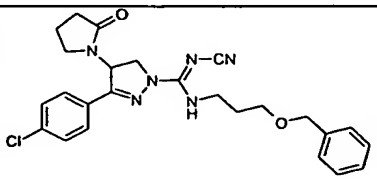
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
358		429	2.58	14
359		452	1.76	14
360		471	2.47	15
361		539	2.75	14
362		471	1.65	14
363		494	2.4	14
364		451	2.04	4

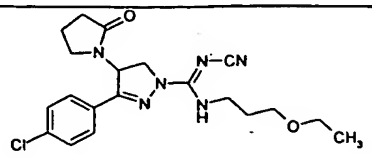
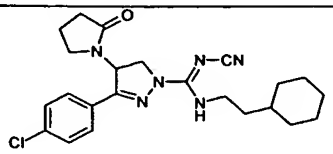
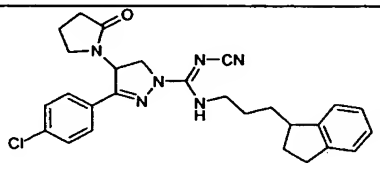
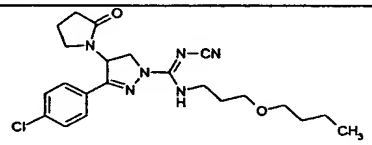
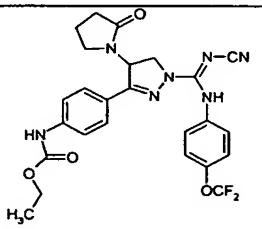
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
365		465	2.11	4
366		485	2.16	4
367		483	2.25	4
368		479	2.02	4
369		538	2.34	4
370		451	2.05	4
371		470	1.5	4

Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
372		465	2.12	4
373		497	2.32	4
374		493	2.13	4
375		435	2.24	4
376		470	1.46	4
377		499	2.05	4
378		534	2.2	4

Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
379		453	2.08	4
380		437	2.04	4
381		471	2.14	4
382		505	2.16	4
383		443	1.99	4
384		475	1.98	4
385		377	2.53	15

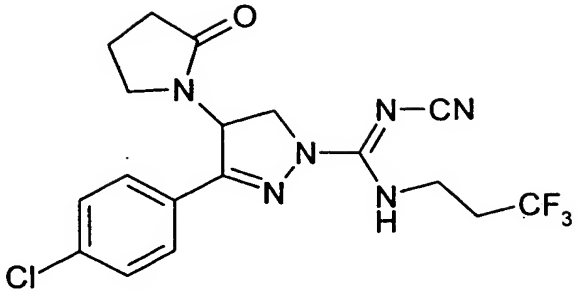
Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
386		431	2.29	14
387		449	2.57	15
388		415	2.45	14
389		454	2.28	14
390		405	2.22	13
391		403	2.15	13
392		403	2.12	13

Example	Structure	m/z [M+H]$^+$	R_t [min]	LC-MS method
393		427	2.30	13
394		426	2.19	13
395		373	2.24	13
396		387	2.39	13
397		505	2.44	14
398		459	2.45	13
399		479	2.55	13

Example	Structure	m/z $[M+H]^+$	R_t [min]	LC-MS method
400		417	2.05	14
401		441	2.87	14
402		489	2.84	15
403		445	2.55	15
404		526	1.98	4

Preparation process for Example 393

3-(4-Chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-(3,3,3-trifluoropropyl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.055 g (0.49 mmol) of 3,3,3-trifluoropropan-1-amine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the precipitate is filtered off and washed repeatedly with diethyl ether. This gives 0.089 g (85% of theory) of the product.

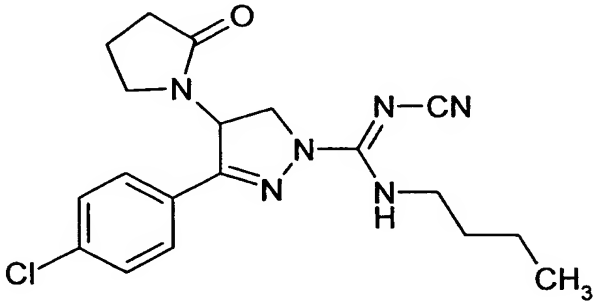
LC-MS (method 13): R_t = 2.30 min,

MS (ESIpos): m/z = 427 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.77 (m, 1H), 1.91 (m, 1H), 2.23 (m, 2H), 2.61 (m, 2H), 2.71 (m, 1H), 3.25 (m, 1H), 3.58 (m, 2H), 4.27 (m, 2H), 6.05 (dd, 1H), 7.58 (d, 2H), 7.76 (d, 2H), 8.04 (t, 1H).

Preparation process for Example 396

N-Butyl-3-(4-chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



0.1 g (0.245 mmol) of phenyl 3-(4-chlorophenyl)-*N*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidoate and 0.035 g (0.49 mmol) of *n*-butylamine are dissolved in 3 ml of ethanol and heated at reflux overnight. After cooling to room temperature, the same volume of water is added, whereupon the product precipitates. After filtration, the product is washed repeatedly with diethyl ether. This gives 0.072 g (76% of theory) of the product.

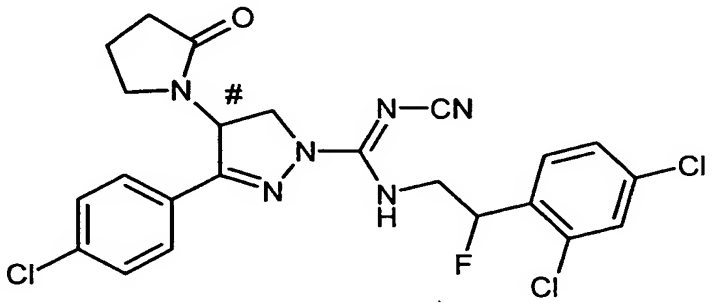
LC-MS (method 13): R_t = 2.44 min

MS (ESIpos): m/z = 387 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.91 (t, 3H), 1.32 (m, 2H), 1.55 (m, 2H), 1.76 (m, 1H), 1.91 (m, 1H), 2.22 (m, 2H), 2.75 (m, 1H), 3.29 (m, 1H), 3.39 (m, 2H), 4.19 (m, 2H), 6.01 (dd, 1H), 7.51 (d, 2H), 7.77 (d, 2H), 7.95 (t, 1H).

Example 405

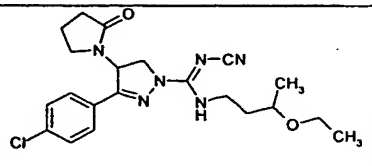
3-(4-Chlorophenyl)-*N'*-cyano-*N*-[2-(2,4-dichlorphenyl)-2-fluoroethyl]-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide

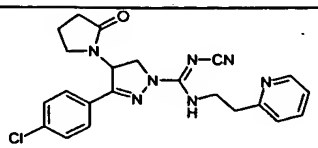
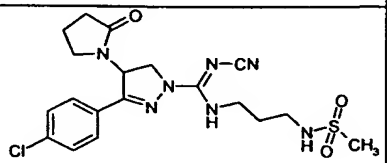
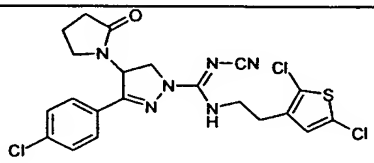
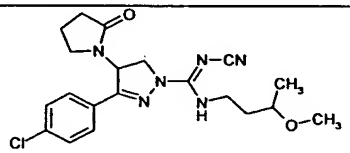
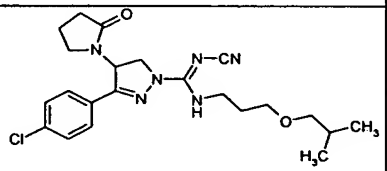
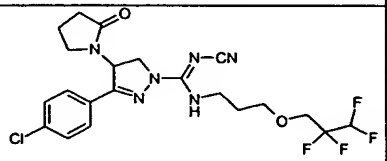
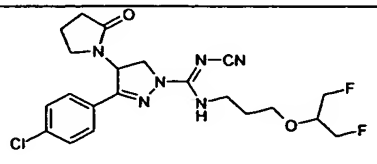


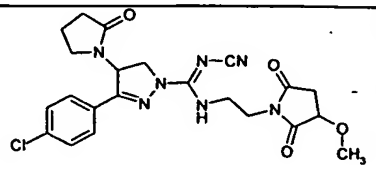
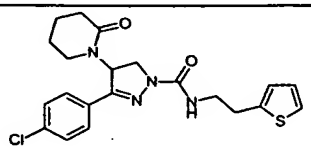
Separation of the enantiomers of Example 354 according to method 17 gives the title compound as enantiomer 2 (>98% ee).

HPLC (method 17): R_t = 5.90 min. (second fraction)

The compounds of Examples 406 to 415 are prepared analogously to the examples described above.

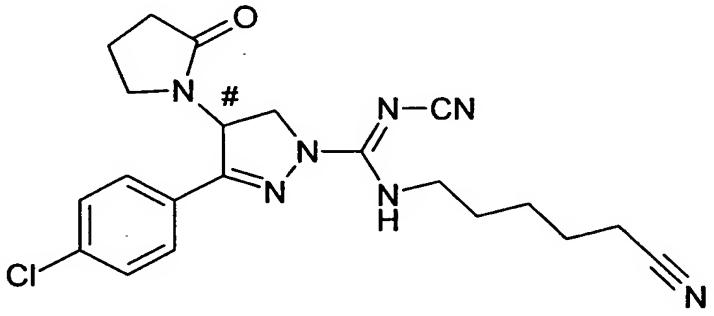
Example	Structure	m/z, $[M+H]^+$	R_t [min]	LC-MS method
406		431	2.34	15

Example	Structure	m/z, $[M+H]^+$	R_t [min]	LC-MS method
407		436	1.64	15
408		466	1.68	14
409		509	2.77	15
410		417	2.26	15
411		445	2.61	15
412		503	2.23	14
413		467	2.24	13

Example	Structure	m/z, $[M+H]^+$	R_t [min]	LC-MS method
414		486	1.96	14
415		431	2.36	14

Example 416

3-(4-Chlorophenyl)-*N'*-cyano-*N*-(5-cyanopentyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide

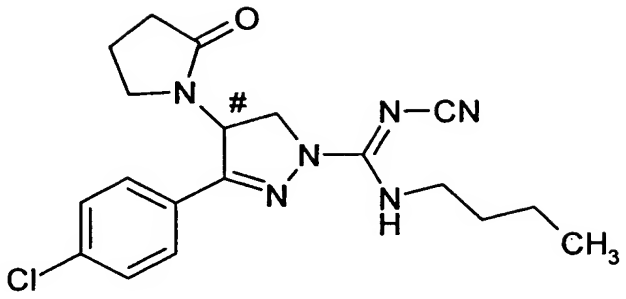


Separation of the enantiomers of Example 394 according to method 21 gives the title compound as enantiomer 1 (> 99.5% ee).

HPLC (method 21): R_t = 6.37 min

Example 417

N-Butyl-3-(4-chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide

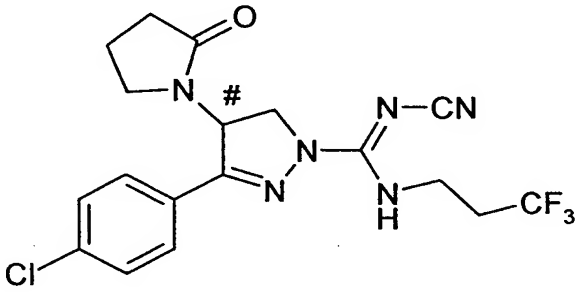


Separation of the enantiomers of Example 396 according to method 22 gives the title compound as enantiomer 1 (> 99.5% ee).

HPLC (method 22): R_t = 5.32 min

Example 418

3-(4-Chlorophenyl)-*N'*-cyano-4-(2-oxopyrrolidin-1-yl)-*N*-(3,3,3-trifluoropropyl)-4,5-dihydro-1H-pyrazole-1-carboximidamide

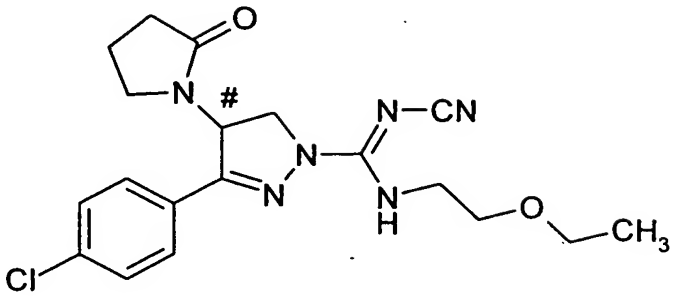


Separation of the enantiomers of Example 393 according to method 22 gives the title compound as enantiomer 1 (> 99% ee).

HPLC (method 22): R_t = 5.14 min

Example 419

3-(4-Chlorophenyl)-*N'*-cyano-*N*-(2-ethoxyethyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide

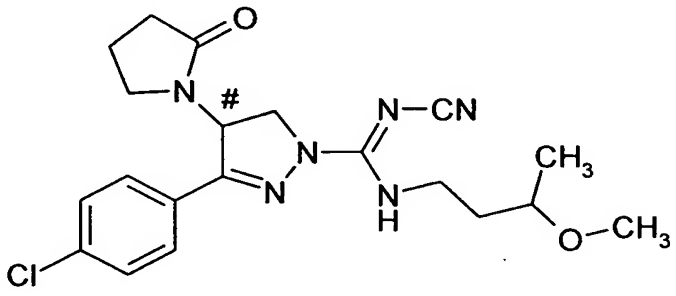


Separation of the enantiomers of Example 391 according to method 22 gives the title compound as enantiomer 2 (> 99.5% ee).

HPLC (method 22): R_t = 11.35 min

Example 420

3-(4-Chlorophenyl)-*N'*-cyano-*N*-(3-methoxybutyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide

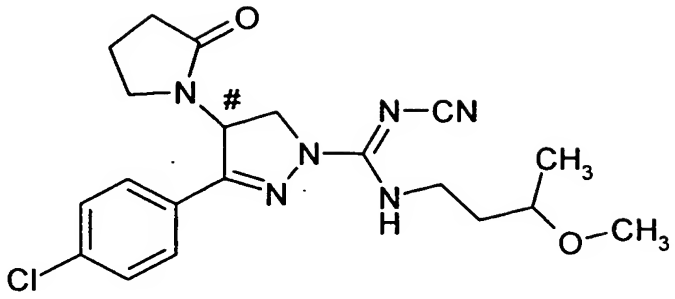


Separation of the enantiomers of Example 410 according to method 22 gives the title compound as enantiomer 1/diastereomer 1 (> 99.5% ee).

HPLC (method 22): R_t = 5.11 min

Example 421

3-(4-Chlorophenyl)-*N'*-cyano-*N*-(3-methoxybutyl)-4-(2-oxopyrrolidin-1-yl)-4,5-dihydro-1H-pyrazole-1-carboximidamide



Separation of the enantiomers of Example 410 according to method 22 gives the title compound as enantiomer 1/diastereomer 2 (> 99.5% ee).

HPLC (method 22): R_t = 6.64 min

B) Assessment of the physiological activity

Abbreviations:

DMEM	Dulbecco's Modified Eagle Medium
FCS	Fetal Calf Serum
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

The suitability of the compounds according to the invention for treating thromboembolic disorders can be demonstrated using the following assay systems:

In vitro assays

a) Cellular functional *in vitro* test

A recombinant cell line is used to identify agonists of the human protease activated receptor 1 (PAR1) and to quantify the activity of the substances described herein. The cell is originally derived from a human embryonal kidney cell (HEK293; ATCC: American Type Culture Collection, Manassas, VA 20108, USA). The test cell line constitutively expresses a modified form of the calcium-sensitive photoprotein aequorin which, after reconstitution with the cofactor coelenterazine, emits light when the free calcium concentration in the inner mitochondrial compartment is increased (Rizzuto R, Simpson AW, Brini M, Pozzan T.; *Nature* 1992, *358*, 325-327). Additionally, the cell stably expresses the endogenous human PAR1 receptor and the endogenous purinergic receptor P2Y2. The resulting PAR1 test cell responds to stimulation of the endogenous PAR1 or P2Y2 receptor with an intracellular release of calcium ions, which can be quantified through resulting aequorin luminescence with a suitable luminometer (Milligan G, Marshall F, Rees S, *Trends in Pharmacological Sciences* 1996, *17*, 235-237).

For testing the substance specificity, its effect after activation of the endogenous PAR1 receptor is compared to the effect after activation of the endogenous purinergic P2Y2 receptor which utilizes the same intracellular signal path.

Test procedure: The cells are plated out two days (48 hours) before the test in culture medium (DMEM F12, supplemented with 10% FCS, 2 mM glutamine, 20 mM HEPES, 1.4 mM pyruvate, 0.1 mg/ml gentamycin, 0.15% Na bicarbonate; BioWhittaker Cat.# BE04-687Q; B-4800 Verviers, Belgium) in 384-well microtitre plates and kept in a cell incubator (96% atmospheric humidity, 5%

v/v CO_2, 37°C). On the day of the test, the culture medium is replaced by a tyrode solution (in mM: 140 NaCl, 5 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 20 glucose, 20 HEPES), which additionally contains the cofactor coelenterazine (25 µM) and glutathione (4 mM), and the microtitre plate is then incubated for a further 3-4 hours. The test substances are then pipetted onto the microtitre plate, and 5 minutes after the transfer of the test substances into the wells of the microtitre plate the plate is transferred into the luminometer, a PAR1 agonist concentration which corresponds to the EC_{50} is added and the resulting light signal is immediately measured in the luminometer. To distinguish an antagonist substance action from a toxic action, the endogenous purinergic receptor is immediately subsequently activated with agonist (ATP, final concentration 10 µM) and the resulting light signal is measured. The results are shown in Table A:

Table A:

Ex. No.	IC_{50} [nM]
41	2
79	3
102	15
119	220
132	4
230	31
297	140
373	130
417	4
418	32

b) Platelet aggregation

To determine the platelet aggregation, blood of healthy volunteers of both sexes who had not received any thrombocyte aggregation-influencing medication for the last ten days is used. The

blood is drawn into monovettes (Sarstedt, Nümbrecht, Germany) which contain, as anticoagulant, sodium citrate 3.8% (1 part of citrate + 9 parts of blood). To obtain platelet-rich plasma, the citrated whole blood is centrifuged at 2500 rpm and at 4°C for 20 min.

For the aggregation measurements, aliquots of the platelet-rich plasma are incubated with increasing concentrations of test substance at 37°C for 10 min. Aggregation is then triggered by addition of a thrombin receptor agonist (SFLLRN) in an aggregometer and determined at 37°C using the turbidimetric method according Born (Born, G.V.R., Cross M.J., The Aggregation of Blood Platelets; *J. Physiol.* 1963, *168*, 178-195). The SFLLRN concentration giving maximum aggregation is individually determined for each donor.

To calculate the inhibitory effect, the increase of light transmission (amplitude of the aggregation curve in %) is determined 5 minutes after addition of the agonist in the presence and absence of test substance, and the inhibition is calculated. The concentration at which the aggregation is 50% inhibited is calculated from the inhibition curves. The results are shown in Table B:

Table B:

Ex. No.	IC_{50} [µM]
41	40
79	5
102	14
119	200
230	12
417	5
418	8

c) Stimulation of washed platelets and analysis in the FACS (Fluorescence Associated Cell Sorter)

Isolation of washed platelets:

Human whole blood is obtained via venipuncture of voluntary donors and transferred into monovettes (Sarstedt, Nümbrecht, Germany) which contain, as anticoagulant, sodium citrate (1 part sodium citrate 3.8% + 9 parts of whole blood). The monovettes are centrifuged at 900 rpm and at 4°C for a period of 20 minutes (Heraeus Instruments, Germany; Megafuge 1.0RS). The platelet-rich plasma is carefully removed and transferred into a 50 ml Falcon tube. ACD buffer (44 mM sodium citrate, 20.9 mM citric acid, 74.1 mM glucose) is then added to the plasma. The volume of the ACD buffer corresponds to a quarter of the plasma volume. The platelets are sedimented by ten minutes of centrifugation at 2500 rotations and 4°C. The supernatant is then carefully decanted and discarded. The precipitated platelets are initially carefully resuspended in one millilitre of wash buffer (113 mM sodium chloride, 4 mM disodium hydrogenphosphate, 24 mM sodium dihydrogenphosphate, 4 mM potassium chloride, 0.2 mM ethylene glycol bis(2-aminoethyl)-*N,N,N',N'*-tetraacetic acid, 0.1% glucose) and then made up with wash buffer to a volume which corresponds to that of the amount of plasma. The washing is then repeated. The platelets are precipitated by another ten minutes of centrifugation at 2500 rotations and 4°C and then carefully resuspended in one millilitre of incubation buffer (134 mM sodium chloride, 12 mM sodium bicarbonate, 2.9 mM potassium chloride, 0.34 mM sodium dihydrogencarbonate, 5 mM HEPES, 5 mM glucose, 2 mM calcium chloride and 2 mM magnesium chloride) and adjusted with incubation buffer to a concentration of 300 000 platelets per µl.

FACS staining and stimulation of the human platelets using human α-thrombin in the presence or absence of a PAR-1 antagonist:

The platelet suspension is preincubated at 37°C with the substance to be tested or the corresponding solvent for 10 minutes (Eppendorf, Germany; Thermomixer Comfort). Platelet activation is triggered by addition of the agonist (0.5 µM or 1 µM α-thrombin; Kordia, the Netherlands, 3281 NIH units/mg; or 30 µg/ml thrombin receptor activating peptide (TRAP6); Bachem, Switzerland) at 37° and with shaking at 500 rotations per minute. After 0, 1, 2.5, 5, 10 and 15 minutes, in each case an aliquot of 50 µl is removed and transferred into one millilitre of singly concentrated CellFix™ solution (Becton Dickinson Immunocytometry Systems, USA). To fix the cells, they are incubated in the dark at 4°C for 30 minutes. The platelets are precipitated by ten minutes of centrifugation at 600 g and 4°C. The supernatant is discarded and the platelets are resuspended in 400 µl of CellWash™ (Becton Dickinson Immunocytometry Systems, USA). One

100 µl aliquot is transferred into a new FACS tube. 1 µl of the platelet-identifying antibody and 1 µl of the activation state-detecting antibody are made up with CellWash™ to a volume of 100 µl. This antibody solution is then added to the platelet suspension and incubated in the dark at 4°C for 20 minutes. After staining, the volume of the batch is increased by addition of a further 400 µl of CellWash™.

A fluorescein-isothiocyanate-conjugated antibody directed against human glycoprotein IIb (CD41) (Immunotech Coulter, France; Cat. No. 0649) is used for identifying the platelets. Using the phycoerythrin-conjugated antibody directed against the human glycoprotein P-selectin (Immunotech Coulter, France; Cat. No. 1759), it is possible to determine the activation state of the platelets. P-Selectin (CD62P) is localized in the α-granules of resting platelets. However, after *in-vitro* or *in-vivo* stimulation, it is translocalized to the outer plasma membrane.

FACS measurement and evaluation of the FACS data:

The samples are measured in the instrument FACSCalibur™ Flow Cytometry System from Becton Dickinson Immunocytometry Systems, USA, and evaluated and plotted using the software CellQuest, Version 3.3 (Becton Dickinson Immunocytometry Systems, USA). The extent of thrombocyte activation is determined via the percentage of CD62P-positive platelets (CD41-positive results). In each sample, 10 000 CD41-positive results are counted.

The inhibitory activity of the substances to be tested is calculated by the reduction of platelet activation, which is based on the activation by the agonist.

Ex vivo assay

Platelet aggregation (guinea pig)

Awake or anaesthetized guinea pigs (strain: Dunkin Hartley) are treated orally, intravenously or intraperitoneally with test substances in suitable formulations. As a control, other guinea pigs are treated in an identical manner with the corresponding vehicle. Depending on the mode of application, blood of the deeply anaesthetized animals is obtained by puncture of the heart or of the aorta for different periods of time. The blood is transferred into monovettes (Sarstedt, Nümbrecht, Germany) which, as anticoagulant, contains sodium citrate 3.8% (1 part of citrate solution + 9 parts of blood). To obtain platelet-rich plasma, the citrated whole blood is centrifuged at 2500 rpm and at 4°C for 20 min.

Aggregation is triggered by addition of a thrombin receptor agonist (SFLLRN, 50 µg/ml) in an aggregometer and determined using the turbidimetric method according to Born (Born, G.V.R., Cross M.J., The Aggregation of Blood Platelets; *J. Physiol.* 1963, *168*, 178-195) at 37°C.

For measuring the aggregation, the increase of the light transmission (amplitude of the aggregation curve in %) is determined 5 minutes after addition of the agonist. The inhibitory activity of the administered test substances in the treated animals is calculated via the reduction of aggregation, based on the mean of the control animals.

In vivo assay

The compounds according to the invention can be studied in thrombosis models in suitable animal species where the thrombin-induced platelet aggregation is mediated via the PAR-1 receptor. Suitable animal species are guinea pigs and, in particular, primates (compare: Kogushi M, Kobayashi H, Matsuoka T, Suzuki S, Kawahara T, Kajiwara A, Hishinuma I, *Circulation 2003, 108 Suppl.* 17, IV-280; Derian CK, Damiano BP, Addo MF, Darrow AL, D'Andrea MR, Nedelman M, Zhang H-C, Maryanoff BE, Andrade-Gordon P, *J. Pharmacol. Exp. Ther.* 2003, *304*, 855-861).

C) **Exemplary embodiments of pharmaceutical compositions**

The substances of the invention can be converted into pharmaceutical preparations in the following way:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch, 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of the compound of Example 1, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. The granules are dried and then mixed with the magnesium stearate for 5 min. This mixture is compressed in a conventional tablet press (see above for tablet format).

Oral suspension:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum) (from FMC, USA) and 99 g of water.

A single dose of 100 mg of the compound according to the invention corresponds to 10 ml of oral suspension.

Production:

The Rhodigel is suspended in ethanol, and the compound of Example 1 is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until the Rhodigel has finished swelling.

Solution which can be administered intravenously:

Composition:

1 mg of the compound of Example 1, 15 g of polyethylene glycol 400 and 250 g of water for injections.

Production:

The compound of Example 1 is dissolved together with polyethylene glycol 400 by stirring in the water. The solution is sterilized by filtration (pore diameter 0.22 µm) and dispensed under aseptic conditions into heat-sterilized infusion bottles. The latter are closed with infusion stoppers and crimped caps.